THE SURGICAL CLINICS OF NORTH AMERICA

DECEMBER 1976

PEPTIC ULCER DISEASE

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THE SURGICAL CLINICS OF NORTH AMERICA

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SYMPOSIUM ON
PEPTIC ULCER DISEASE

Avram M. Cooperman, M.D., *Guest Editor*

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AVRAM M. COOPERMAN, M.D.,
Guest Editor

Foreword

The last symposium on peptic ulcer disease in *Surgical Clinics of North America* was published in 1971. Although there has been steady if unspectacular progress in the treatment of this disease since 1881, truly new concepts and methods of both medical and surgical treatment have emerged in the past 5 years.

The incidence of peptic ulcer disease is decreasing, but the etiology and pathogenesis remain largely unknown. Even the natural history characterized by exacerbations and remissions is not well understood. Hopefully this new knowledge will provide a more scientific basis for medical and surgical treatment.

The limitations of conventional treatment including diet, antacids, and anticholinergics are well known to ulcer patients and their physicians. However, the isolation and use of histamine (H_2) receptor antagonists has for the first time provided a potent, promising, and simple regimen for ulcer patients, apparently without significant side effects. These drugs, metiamide and now cimetidine, effectively reduce gastric secretion and permit healing of most duodenal ulcers, even in some patients with the Zollinger-Ellison syndrome. Perhaps the era preceding the release of cimetidine (if it proves as effective as hoped) will in the new ulcer theology be called B.C. (Before Cimetidine). B.C. is not to be regarded as an irreverent comparison, but as a means of emphasizing the revolutionary potential of this drug.

As improved medical treatment becomes available, it will become more important for surgeons to assess their results with great objectivity, because referring physicians will be even more reluctant to subject their patients to ulcer operations.

An operation based on physiologic principles that minimally alters gastric physiology has created considerable interest.

Johnston, Goligher, and Andrup have made American surgeons aware of the possible advantages of proximal gastric (highly selective) vagotomy. Its position in 1976 is summarized in this volume both by its practicing advocates and by experienced surgeons who have witnessed several other ulcer operations come and go.

In this volume methods for testing the completeness of vagotomy are reviewed. "Facts and heresies" about vagotomy are also summarized.

Over the past 5 years, postvagotomy and postgastrectomy sequelae have been separated so that some syndromes (alkaline reflux, dumping, and diarrhea) can be treated more effectively when necessary.

The use of angiography in the diagnosis and treatment of bleeding duodenal ulcers has become available and popular during the past 5 to 10 years. Surgeons can now utilize endoscopy and angiography for the location and control of acute ulcer hemorrhage.

The contributors to this symposium are physicians and surgeons interested in peptic ulcer disease. Some are internationally known and their wisdom and experience are accurately recorded. Others, perhaps less well known but equally interested, have thoughtfully summarized their topics.

The atmosphere and staff of the Mayo Clinic first stimulated my interest in ulcer disease and gastrointestinal physiology, particularly Charles Code, Keith Kelly, John Kirklin, James Priestly, and George Hallenbeck. Subsequently, my colleagues, Stanley Hoerr and George Crile, Jr. have continued to question and stimulate my thinking. I thank all of these men.

I offer my thanks to each contributor for the quality of his paper and for meeting the assigned deadline (or by not missing it by too much). My gratitude is extended to my severest critics; my wife Jacqueline, who edited my editing of each manuscript and to Rita Feran, publications editor of the Cleveland Clinic, who painstakingly re-read and re-edited each manuscript. To Renee Gutman who traced the earlier references I extend gratitude. The secretarial assistance of Mrs. Carrie Harris is appreciated as well.

Finally, my thanks to the *Surgical Clinics* and its editor Mr. Paul Dolgert for the opportunity to present this material.

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Pathogenesis and Medical Treatment of Peptic Ulcer Disease

"The significance of an ailment should not be measured by the inconvenience it causes at the time, but by what may come of it four or five years afterward."

Charles H. Mayo, Proc. Interstate Postgraduate M.A. North America, Oct. 19–23, 1931, pp. 245–248.

"In medical progress the means of relief by therapeutic measures or surgery have far outstripped our knowledge of the cause of disease."

Charles H. Mayo, Ann. Surg., 7:123–217, 1920.

"Unfortunately only a small number of patients with peptic ulcer are financially able to make a pet of an ulcer."

William Mayo, J.A.M.A., 79:19–22, 1922.

The Natural History of Duodenal Ulcer Disease

*George A. Hallenbeck, M.D.**

The phrase "duodenal ulcer" is self-explanatory. Most duodenal ulcers occur in the duodenal bulb, the part just beyond the narrow pyloric channel through which gastric contents enter the duodenum. Duodenal ulcer that develops in people usually heals, and there may be a few individuals who never get another. Most patients, however, have ulcers recur over the years, some often and some infrequently. We can speak of these as having the "duodenal ulcer diathesis," a phrase that reminds us of the chronicity of the disease but tells us nothing about its pathogenesis. Some ulcers occur distal to the duodenal bulb, some in the pyloric channel proximal to it, and some large ulcers spill over into the gastric antrum. Presuming that these share a common if incompletely understood pathogenesis, we may lump them together conveniently as expressions of "duodenal ulcer disease."

It is hard to believe that duodenal ulcers have not been with man throughout his history, but although gastric ulcers were described often in the early literature, duodenal ulcers received little attention until the 20th century. Wilbur[28] notes that John Abercrombie of Edinburgh described duodenal ulcers and their symptoms quite clearly in 1828, but when Perry and Shaw reviewed 1765 autopsies performed at Guy's Hospital from 1826 to 1892, they found active duodenal ulcers or duodenal scarring mentioned in only 0.4 per cent.

As asepsis and improvements in anesthesia made abdominal surgery feasible, intra-abdominal lesions began to be seen at earlier stages of development and surgeons could correlate clinical with pathologic findings. Moynihan in Leeds and the Mayos in this country were among the first to take advantage of this opportunity in the case of peptic ulceration, and to Moynihan[16] goes much of the credit in the first decade of the 20th century for calling attention to the apparently increasing frequency of duodenal ulceration and for emphasizing the clinical sequence of pain-food-ease, the frequent similarity of pain to hunger, and the tendency to remissions and exacerbations. Whatever the situation may have been previously, duodenal ulcers have exceeded chronic gastric ulcers in England and the United States of America in the 20th

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century by about 4 to 1. Some reports from Scandinavia, such as that of Norbye in 1952, however, show that in Norway from 1926 to 1940, the ratio of the duodenal to gastric ulcers in men was only 1.95 to 1, and in women, 0.77 to 1.

INCIDENCE AND PREVALENCE

Walker,[24] summarizing British autopsy data collected by Watkinson,[27] information from a private practice in Britain,[6] a United States National Health Survey based on a sample of 235,000 people,[1] and a survey of physicians in Massachusetts,[15] found the annual incidence of active duodenal ulcer to be 2 per cent of males and 0.5 per cent of females aged 30, and 3 per cent of males and 1 per cent of females over 40 years of age.

Duodenal ulcers come and go in individuals, hence the prevalence, i.e., the percentage of population with active or inactive disease, is higher, rising gradually to about 10 per cent in males at 50 years of age and to about 4 per cent in females who have reached 40 years of age. At least this seems to have been a fair approximation of the case in industrialized countries up to about 1960. Recently, studies by Susser[21] and by Meade and associates[13] in England and by Mendeloff[14] in the United States show the incidence of duodenal ulcer disease to have declined in these countries by 40 to 50 per cent. The meaning of all this is unclear, and one could wish, as Mendeloff does, for better record keeping and a better national system for relating clinical data to population analysis and retrieving results promptly, but the news will not surprise many who think they are not seeing as many new duodenal ulcers as they did 10 to 15 years ago.

CLASSICAL UNCOMPLICATED DUODENAL ULCER DISEASE

The patient, rarely in his teens, fairly often 20-29, and most frequently 30–39, 40–49, or 50–59, develops dyspepsia with certain characteristics obtainable through history alone that permit duodenal ulcer to be suspected with a high probability that the diagnosis will prove to be correct.

There is visceral pain, epigastric in location, deep and usually in the midline, sometimes just below the xiphoid process, and sometimes at various levels between that point and the umbilicus. Despite the fact that visceral pain is usually poorly localized, the patient often indicates the site of his duodenal ulcer pain with one finger. He may not think of it as pain and may use any of several words, such as aching, burning, gnawing, boring, a hungry feeling, or just that old catch-all, "gas," to describe it. It is important to discover the patient's code word for the discomfort early in the interview to establish communication about it, but the name of the pain is less important than its characteristics.

This pain comes and goes, relieved temporarily by eating, and reappearing 2 or 3 hours later when the buffering effect of food on gastric contents has been overcome by acid secreted in response to the meal. Often gastric pH decreases during the night, fairly early if the patient goes to bed without eating a bedtime snack and later if he drinks milk or eats lightly before retiring, and though he goes to sleep he may be wakened by pain. By morning, enough time has passed since the last feeding that gastric acid secretion is reduced, and pain that occurs before breakfast is unusual enough to cast doubt on the diagnosis of duodenal ulcer disease.

The pain is also relieved promptly, though temporarily, by antacids, a fact picked up by all but the least discerning patients in this day of national advertising, and when one is trying to learn what makes the pain better, he must remember to ask about the many antacid preparations sold over the counter as well as those that might have been prescribed.

Lastly, the ulcers form and heal, and the symptoms thus come and go, sometimes lasting only a week or so and sometimes several weeks. This periodicity, as it is called, is an important diagnostic feature that can be elicited in most cases if it is sought. One of the mistakes made by students beginning to learn about ulcer disease is to accept without question the patient's statement that he got sick "last Tuesday," thereby missing 25 years of recurrent dyspepsia.

Thus, the diagnosis of typical duodenal ulcer disease is, as usual, a matter of pattern recognition. Once one hears enough to think of duodenal ulcer disease he asks, with great care not to salt the mine, the proper questions to learn whether his patient does in fact have epigastric pain when he has not eaten for a few hours, pain that is relieved by food or antacids, that may awaken him from sleep at night, and that occurs periodically in spells of a week or more rather than continuously or for just a few hours or a day at a time.

The severity of the duodenal ulcer diathesis varies considerably from patient to patient. In some, attacks of ulcer pain are infrequent with years between episodes; in others, the disease behaves more aggressively with attacks occurring several times a year, lasting longer, and with complications appearing early in the course of the disease. In six of seven studies published between 1932 and 1971 and collected by Palmer,[19] the disease recurred within 5 years in from 64 to 86 per cent of cases; in the remaining study, in 46 per cent of cases. The natural history of the disease is not known well in quantitative terms, but broadly speaking, about 75 to 80 per cent will have recurrent symptoms within 5 years after the first documented episode of duodenal ulceration and, although the disease often seems to wane as patients grow old, this is by no means always the case, and active aggressive ulcers are often seen in the elderly. I think patients should be informed after their first diagnosed attack that they probably will continue to have a tendency to form duodenal ulcers. Armed with this knowledge, they can often recognize recurrence early and, by initiating a simple medical regimen—cleaning up their act, so to speak—avoid much of the discomfort that would otherwise have been present during the healing process.

VARIATIONS ON THE THEME

Asymptomatic Ulcers

Acute perforation of duodenal ulcers or bleeding attributed to duodenal ulcer occurs in patients who deny any previous ulcer-like symptoms. This, plus the occasional finding of radiologic evidence of duodenal ulceration or deformity of the kind usually seen after duodenal ulceration in patients without an appropriate history, indicates that in some people duodenal ulcers may be asymptomatic. Whether this phenomenon results from indifference to or an unusually high threshold to pain or to undetermined physiologic variations in perception of pain is speculative. In any case, lack of an ulcer history does not exonerate peptic ulceration in evaluation of the patient with a spontaneously perforated viscus or with upper gastrointestinal bleeding.

Altered Pain Pattern with Chronic Perforation

When duodenal ulcers penetrate through all layers of the duodenum so that the base of the ulcer becomes the pancreas, liver, or biliary tract, somatic pain usually appears that is often referred to the lower thoracic and upper lumbar region in the back and sometimes to the right upper quadrant of the abdomen. This pain is less completely and more briefly relieved by food and antacids than is the visceral pain of duodenal ulceration, and periodicity of symptoms often disappears because such ulcers heal slowly, if at all. These penetrating ulcers commonly are among those so intractable to nonsurgical management that operation is indicated.

Postbulbar Duodenal Ulcers

In probably no more than 3 or 4 per cent of cases, ulcers occur in the distal third of the first portion of the duodenum or even in the second portion. Often such ulcers are missed in the first gastroduodenal x-ray examination and found only later by repeated radiologic, or commonly nowadays, by endoscopic means. The atypical location should make one check for Zollinger-Ellison syndrome, but most patients with single postbulbar ulcers in the duodenum will have variants of the ordinary duodenal ulcer diathesis. These ulcers may have symptoms similar to those of patients with ulcers in the duodenal bulb, but in many the pain may be in the right upper quadrant and the back, pain at night is unusually frequent, response to nonsurgical treatment is poor, and the incidence of bleeding and obstruction is high. The surgeon, looking for a source of bleeding or for an organic cause of vomiting, should not forget postbulbar duodenal ulceration when more obvious causes are not found, because these lesions, when small, can be overlooked easily.

Pyloric Channel Ulcers

The narrowest part of the gastric outlet, surrounded by the pyloric sphincter and extending from the beginning of the duodenum proximally for 1 to 2 cm, can usually be well demonstrated radiologically and may be the site of peptic ulceration. Although pyloric channel ulcers may

behave symptomatically like duodenal ulcers, they are often less responsive to the palliative effects of diet and antacids. Indeed, eating may accentuate the discomfort which is best relieved by vomiting. Symptoms persist longer and recur more often than with most ulcers of the duodenal bulb. As a result, pyloric channel ulcers tend to require surgical treatment earlier than the average bulbar duodenal ulcer.[5, 17, 22]

Gastroduodenal Ulcers

Sometimes larger ulcers involve the entire gastroduodenal junction and these, by virtue of pyloric obstruction, bleeding, or failure to heal often require surgical treatment. In other cases separate ulcers may be present in the duodenum and in the prepyloric area, and the sequence here is often one of repeated duodenal ulceration occurring to the point of incomplete pyloric obstruction with the prepyloric gastric ulceration following.

It is important to recognize that gastric ulcers occurring in this setting are part of the duodenal ulcer diathesis. When surgical treatment becomes necessary it should be that for duodenal ulcer disease, avoiding hemigastrectomy with gastroduodenostomy unless vagotomy is done because although gastric resection alone with the Billroth-I reconstruction is a good procedure for primary gastric ulcer, it is followed by a high recurrence rate when used for duodenal ulcer disease.[2, 26]

COMPLICATIONS OF DUODENAL ULCER

Since we consider that surgical treatment is indicated not by the mere existence of duodenal ulcer but by the development of one or more of its complications, a review of these complications is in order.

Bleeding

Ivy and associates[19] reviewed the literature extensively and concluded that bleeding occurs in 25 per cent of patients with duodenal ulcer who are admitted to hospitals. Walker,[25] reviewing four extensive studies,[3, 6, 12, 18] considered it reasonable to assume that 15 to 20 per cent of patients with gastric ulcer will have had at least one hemorrhage during 15 to 25 years of follow-up. Such figures tell us that manifest bleeding is common but do not relate its prevalence to the duration of the disease. Stolte[20] in Amsterdam charted the dates of onset of ulcer symptoms and of the first manifest bleeding in 333 patients with duodenal or gastric ulcers and found that the percentage of patients who had bled at least once to some degree, great or small, increased steadily from about 37 per cent at 5 years to 86 per cent at 30 years! Whether the behavior of duodenal ulcers in the United States today would be similar we cannot say, but the data do emphasize the persistent nature of the duodenal ulcer diathesis mentioned before.

It is commonly taught that some patients with duodenal ulcer are more likely to bleed than others and may bleed again and again. Data from many reports support this observation in a general way.[7] Chinn et al.[4] determined the risk of subsequent bleeding in 310 patients with

duodenal ulcer who had their first hemorrhage at the University Hospital in Cleveland. The risk of subsequent bleeding increased gradually from about 23 per cent after 3 years to 48 per cent at the tenth year. The chance of having a second hemorrhage was not affected by age, although bleeding is more often lethal in the aged than in younger people. Looking at the data another way, one can say that about one-third of duodenal ulcer patients who had bled once previously, bled again within 5 years; and about two-thirds of those who had bled twice previously had a third hemorrhage within 5 years.

In general, the data support the propositions that gross bleeding of some degree is common among patients with duodenal ulcer and that some patients have a predisposition to hemorrhage, the cause of which is not understood.

Acute Perforation

When ulcers extend through the entire wall of the duodenum rapidly enough that the resulting opening cannot be sealed by adhesions to surrounding structures, duodenal contents leak into the peritoneal cavity, causing the familiar sudden onset of severe and usually generalized abdominal pain, prostration, abdominal rigidity, and pneumoperitoneum. Sites of free perforation are determined by the anatomy of the duodenal bulb and are primarily anterior rather than posterior, where the duodenal bulb is protected by its attachment to the pancreas.

The reported prevalence of acute perforation in series of patients with duodenal ulcer disease varies remarkably in different parts of the world, as Haubrich[8] has pointed out, but ranges from 5 to 10 per cent in this country. It has been estimated that about 7.5 per cent of acute free perforations occur in patients who give no history suggestive of previous duodenal ulceration.[23]

Once free perforation of a duodenal ulcer has occurred and been closed surgically, about 70 per cent of patients have further trouble with ulcer symptoms later. In the experience of Jordan, Debakey, and Duncan,[10] the figure was 73 per cent of 63 patients, 22 of whom subsequently underwent definitive operation. They, like others, have often used simple closure for patients who give no previous history of ulcer symptoms, but they note that even among these patients, half have had recurrent symptoms. I think it makes sense to base surgical decisions on the assumption that acute perforation is evidence that an aggressive ulcer diathesis is present, and to carry out a definitive operation when, with all factors considered, the risk is expected to be low.

Obstruction

Pyloric obstruction may have many different causes. We are concerned here with that caused by duodenal ulcer. Obstruction has been reported to occur in about 10 per cent of patients hospitalized for duodenal ulcer disease.[25]

Usually obstruction is preceded by a long and classic history of the disease: ulcers in the narrow pyloric channel may cause obstruction earlier. Vomiting, the most common symptom of pyloric obstruction, constitutes a change in the symptoms, dominating and sometimes replacing

ulcer pain. Eating, which formerly gave some relief, may now cause discomfort in the form of unpleasant fullness to be relieved by vomiting. Relief after antacids is less complete than formerly. Because eating is followed by distress, intake of food tends to decrease and, of course, some is lost by vomiting. Loss of weight results. If the rate of development of obstruction is slow, the patient may gradually develop gastric dilatation and atony, and finally a huge, edematous, thick-walled stomach that may accommodate such volume that vomiting occurs only once or twice in the evening, the patient having been fairly comfortable in the morning and filling gradually to discomfort as the day progresses. Especially in these cases, the patient may recognize in the vomitus food eaten 24 or more hours previously.

Losses of water, sodium, potassium, and chloride lead to decreased extracellular fluid volume with hypochloremic, hypokalemic alkalosis which must be corrected before an operation is considered.

Duodenal ulcer disease causes pyloric obstruction by a combination of edema associated with acute inflammation, spasm, and permanent narrowing due to fibrosis. When edema predominates, obstruction may recede after 2 or 3 days of nasogastric suction, during which time the metabolic alkalosis is corrected by intravenous administration of water and appropriate electrolytes, and remission of obstructive symptoms may occur. When fibrosis predominates and obstruction is of long standing or when reasonable attempts to get large duodenal or gastroduodenal ulcers to subside fail, surgical treatment is necessary.

Intractability

Intractability is often the most frequently given indication for surgical treatment of duodenal ulcer. At first glance, it is easy to define: failure of the ulcer to be controlled to a degree that permits a satisfactory life despite standard medical treatment. The term fits well the deep posterior penetrating ulcer with a scarred base that, one can imagine, provides little vascular support for tender epithelium that may from time to time try to cover it. Large gastroduodenal ulcers causing incomplete pyloric obstruction, pyloric channel ulcers, and postbulbar ulcers also may lose the periodicity that comes from intermittent healing, and in these cases the patient's life revolves about nearly continuous ulcer activity. Ulcers of these kinds constitute a large percentage of those judged intractable and thus surgical.

The designation, intractable, remains subjective, however, and may be interpreted to include inability or unwillingness to follow an orderly life that might permit control of symptoms. The decision to recommend surgery on the basis of intractability is an important one. There is evidence that people with character neuroses, alcoholism, and little stimulus to become involved in life and work tend to get poor results from surgical treatment.[11]

Finally, we may ask what percentage of unselected patients with duodenal ulcer come to need surgical treatment? Figures of 15 to 20 per cent are quoted commonly, but these are usually selected in the sense that they belong to a large group that had enough trouble to get diagnosed. We really don't know what the denominator is, but I suspect that

the true percentage of duodenal ulcers that are surgical is much smaller than is usually quoted. When a good H-2 blocking drug comes on the scene and reaches general use, the figure probably will be even lower.

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Facts, Anecdotes, and New Horizons in the Medical Treatment of Duodenal Ulcers

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The treatment of duodenal ulcer disease continues to be based on scattered facts cemented together with anecdotes and beliefs. There is frequently agreement on the facts themselves, but the way they are arranged and the anecdotes used to fill the gaps have led to marked differences in the way duodenal ulcer patients are treated. We know that a given antacid will relieve pain and neutralize a given amount of acid, and we know that acid is an essential part of the peptic ulcer diathesis. We also know that certain antacids can stimulate gastric secretion, produce diarrhea, bind phosphate in the gut, mobilize calcium from bone, and interfere with the absorption of drugs and nutrients. What we are not able to do is to put the facts together in a way that will be generally agreed upon. We would like to be able to say that taking an antacid, an anticholinergic, or some other agent in a given dose for so many days or months will produce benefits in the quality and length of life which clearly outweigh the results of not taking the agent at all or taking it in some other way. It is rare to be able to make this sort of statement based on conclusive data, and it is usually necessary to fill in for the absent facts with opinion and belief.

The same dilemma applies to other medical approaches as well as to surgical therapy. We can, for instance, compare the operative mortality of different procedures and examine recurrence rates and side effects of different operations. However, when we want to know whether a given elective operation clearly improves the quality and duration of life when compared to other operations or no operation, the inadequacy of the facts becomes very apparent. It is not for lack of effort that our information is incomplete, and studies are underway to try to answer the remaining questions. Proposals for altering our current state of ignorance have been examined in detail in a recently published paper.[7]

Before evaluating the status of medical therapy of peptic ulcer, let us look at some new developments and then proceed to the issue of the

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failure of medical therapy (intractability) and to an examination of some reasons why it appears so difficult to know just how good (or bad) a given treatment scheme may be.

NEW HORIZONS

The most promising development in the management of peptic ulcer disease has been the discovery of a new class of drugs, the antagonists of the H_2-receptors of histamine. Several other drugs are also being evaluated and advances in endoscopic and angiographic techniques appear to hold promise for the control of bleeding. Extensive prospective trials of some of the conventional medical therapies are in progress and may finally provide more definitive answers about the effectiveness and hazards of the older methods of managing peptic ulcer disease.

Antagonists of the H_2-Receptors of Histamine

When the first class of histamine antagonists was developed about 30 years ago, it soon became apparent that they were capable of blocking some effects of histamine such as allergic edema and itching. However, these older antihistamines were totally ineffective in controlling some other effects of histamine, including the stimulation of gastric secretion. The persistence of J. W. Black and his colleagues has led to the development of a new group of drugs which block the effects of histamine on the stomach.[2] We assume that since there are two kinds of histamine antagonists, there must be two kinds of histamine receptors. The first kind of receptor is called H^1 and is antagonized by the familiar antihistamines such as dyphenhydramine (Benadryl) and chlorpheniramine. The second kind of histamine receptor, the one responsible for gastric secretion is called an H_2 receptor, and this is blocked by the new class of antihistamines of which metiamide and cimetidine have been studied most extensively. Unfortunately, metiamide, the first oral preparation tested, has led to instances of agranulocytosis, a problem believed to be related to the thiourea group in this drug. A newer oral agent, cimetidine, does not contain a thiourea group and so far has been free of side effects. These agents are not yet marketed in this country. Extensive clinical trials are underway, and enthusiasm for cimetidine is great, to say the least. Cimetidine blocks the effects of all the stimuli of gastric secretion such as gastrin, feeding, and hypoglycemia. It is believed by many that the introduction of these drugs will revolutionize the management of peptic ulcer disease.

Prostaglandins

Since the discovery, in the 1930s, of biologically active fatty acids from the prostate gland (hence the name prostaglandin), it has become clear that similar substances appear in practically every tissue and fluid in the body. Minute amounts of these local hormones are capable of altering almost every biologic function, and they are produced in response to a wide spectrum of stimuli. Prostaglandins of the types known as E_1

and E_2 (PGE_1 and PGE_2) inhibit basal as well as histamine, pentagastrin, and meal-stimulated gastric secretion in man. Analogs of these prostaglandins which can be taken orally have been developed. They are under study, and preliminary reports suggest that the oral forms do in fact inhibit gastric secretion[10] and may accelerate the healing of peptic ulcer.[5] Because the spectrum of biologic activity is so broad for these compounds, we will need much more information on side effects as well as the necessary controlled therapeutic trials of efficacy before deciding whether or not to endorse them.

Other New Drugs

Other agents which have aroused interest but are not yet available or not widely used include gastrointestinal hormones, carbenoxolone, and bismuth. These agents merit study and have been reviewed recently, but their usefulness and safety remain to be demonstrated.[6]

Endoscopic Advances

The management of gastrointestinal hemorrhage has been changing as a result of the expanding capabilities of endoscopic instruments. The improvement in diagnosis is well established, but recent advances in what can be done through a fibreoptic instrument have been decreasing the number of uncontrollable hemorrhages, and the future looks even brighter. It is becoming possible to control bleeding with electrocautery as well as with the topical application or transmucosal injections of hemostatic agents. Photocoagulation of bleeding lesions with laser beams is being studied. These techniques have been reviewed recently.[11]

The use of selective angiography for identification as well as control of upper gastrointestinal bleeding is effective and becoming increasingly available.

INTRACTABILITY: THE FAILURE OF MEDICAL MANAGEMENT

A small group of patients with duodenal ulcer disease fail to respond to all reasonable medical measures and the disease or its treatment disrupts the ability to function and enjoy life. Surgical procedures continue to offer much for many of these people. However, before deciding to label an ulcer intractable, care should be taken to make certain that it is the ulcer that is intractable rather than the patient, the physician, or the medical regimen. There may be some place for the use of traditional, unpalatable diet therapy ("slops I, white mush II, and bland tastelessness III," as they have been described by Ingelfinger[9]). However, when a patient says that he would rather have surgery than continue living on farina, cream of wheat, and antacids while his friends eat steak and pizza, it may be reasonable to let him eat the things he wants before proceeding to surgery. A number of patients who have been declared intractable appear to lose interest in surgery when they discover that they

can resume eating food that has some taste. The mythology of the "white diet" in the management of ulcer disease has been described by Ingelfinger.[8]

Other things to be considered in patients who at first appeared intractable include an examination of the remedial contributing causes. Is the patient ingesting aspirin in some form? Is he taking aluminum-magnesium antacid so regularly that he has persistent diarrhea or recurrent muscle weakness? Is he taking a calcium antacid which is stimulating gastrin production and gastric secretion so that the agent which temporarily relieves his pain is also responsible for the continuation of his peptic ulceration? Has the vigorous use of anticholinergics or tranquilizers altered his mental and neurologic state so that he is unable to see and think clearly? These questions may lead to simple readjustments in therapy which will solve the the intractability problem for many patients.

Alternatively, patients who have been treated with a very liberal or permissive program may benefit from more rigidity. The response of some patients to the laissez-faire approach may be a feeling that they and their disease are not being taken seriously. The attention they seek in their request for an operation may be provided by a physician willing to listen to their troubles and outline a more intensive program of medical management.

In addition to these measures, the intractable patient should of course be checked for gastrinomia and other endocrine abnormalities, especially hyperparathyroidism. A brief trial of hospitalization and nasogastric suction may be useful, and a search should certainly be made for penetration of the ulcer or coincident pancreatitis. A commonly overlooked abnormality, painful costal cartilages (so-called costochondritis) may confuse the physician and will probably continue to be a problem after surgery. This entity may be especially confusing if the patient in an attempt to immobilize the tender cartilages contracts his abdominal muscles which results in spasm, pain, and tenderness in the upper rectus abdominus muscles. Palpation of the cartilages may provide the diagnosis, and a trial of local injections of corticosteroids or the use of more potent oral anti-inflammatory agents may relieve symptoms that were incorrectly assumed to arise from the gut. A detailed description of approaches to intractability has been provided by Spiro.[14]

THE ORIGINS OF THE MYTHS AND ANECDOTES

Why should it be so difficult to develop a treatment program for duodenal ulcer disease that will be accepted by most reasonable people? If we look at antacid use, there is argument not only over which antacids but over whether to use them at all. Some physicians vigorously advocate their use only for the relief of pain, others argue that very large but infrequent doses should be used for weeks beyond the relief of pain, and others argue that very frequent but smaller doses provide the most

reasonable approach.[3, 6, 12, 13] The argument over the use of anticholinergics continues. Should they be used at night only, night and day continually, or avoided?[1, 4] That there is dispute over when to operate and which operation to perform is attested to by this volume of papers and a very large and contentious literature.

Why the disagreement? Why do some physicians believe so strongly in modes of therapy that are rejected by others? I suspect that the major problem lies in the fact that most duodenal ulcer patients do quite well without vigorous intervention and that most episodes of peptic ulceration will cease despite the therapy employed.[4, 15] This is not to say that we should take lightly the very serious complications of ulcer disease. Certainly perforations, uncontrolled bleeds, irreversible obstructions, and severe disabling pain require vigorous intervention. However, the tendency of most episodes of peptic ulceration to subside spontaneously and the tendency for the disease to run its course, so that after 15 years about 90 per cent of duodenal ulcer patients are either free of disease or minimally symptomatic[4] creates some problems in interpreting one's "experience." If the disease tends to remit and to eventually burn itself out it is easy to take credit for the cure. If, for instance, 80 per cent of patients are in relatively good health after a course of antacid therapy or after vagotomy and pyloroplasty, it is likely that the person who advocated the treatment will tend to take credit for these eight of ten who did well and to believe that his therapeutic decision was responsible for the happy results. Without precise, long-term, thorough studies these anecdotal memories tend to have a marked effect on practice. It is probable that the great differences in therapeutic programs stem from the fact that most duodenal ulcer patients will do quite well providing we do not institute outrageous and detrimental maneuvers.

I do not wish to make the case for therapeutic nihilism, but rather to point out that much of what is vigorously advocated in the management of duodenal ulcer disease may arise from conclusions based on observations that are not entirely sound. The answers lie obviously in careful long-term evaluations of the various treatments, and our goal must be to constantly revaluate our therapies to avoid making things worse in spite of our good intentions.

SUMMARY

There continue to be marked differences of opinion regarding how to manage duodenal ulcer disease. Recent developments in medical management which appear of major importance include the development of antagonists of H_2-receptors of histamine, the prostaglandins, and transendoscopic instrumentation. Intractability of duodenal ulcer continues to be an over-used category which disguises situations that are easily remedied. Until we have more long-term and complete evaluations of ulcer treatment, we will continue to base therapy on anecdotes and incomplete data.

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Gastrin and Ulcer Disease: What Is Known

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In 1905, Edkins[38] proposed gastrin as the hormone which stimulates gastric secretion, but contamination with histamine clouded the issue. In 1938, Komarow[75] produced a histamine-free extract of gastrin, thus confirming its existence, but it is the past decade that has witnessed a rapid explosion of interest in gastrin. This has resulted from three main factors:

1. The preparation of a pure gastrin extract from hog's antrum by Gregory and Tracy in 1964.[59]
2. The synthesis of the hormone[1, 56, 130] along with a number of smaller but highly active fragments such as the C terminal pentapeptide, "pentagastrin."[84]
3. The development of a sensitive and specific method of measuring the endogenous hormone: namely, the use of radioimmunoassay techniques.[8, 89, 91, 150]

STRUCTURE

Gregory and Tracy's gastrin extract[59] was a polypeptide with a molecular weight of 2114 containing 17 amino acid residues which they named gastrin I and II, the difference between the two being a sulfated tyrosine molecule at the 12 position in gastrin II (Fig. 1). Yalow and Berson's[151] fractionation studies resulted in isolation of a larger molecular form of gastrin, which they called big gastrin, as the main form of plasma immunoreactive gastrin in patients with pernicious anemia and Zollinger Ellison (ZE) syndrome. The amino acid sequence of big gastrin was subsequently determined by Gregory and Tracy,[58] who found 34 amino acid residues (G34) as opposed to the 17 amino acid residues of "little gastrin" (G17), which in fact is the C terminal[18-34] fraction of G34. The third naturally occurring human gastrin has 13 amino acid residues (G13), and is aptly known as a "mini" gastrin. Isolated by Gregory and

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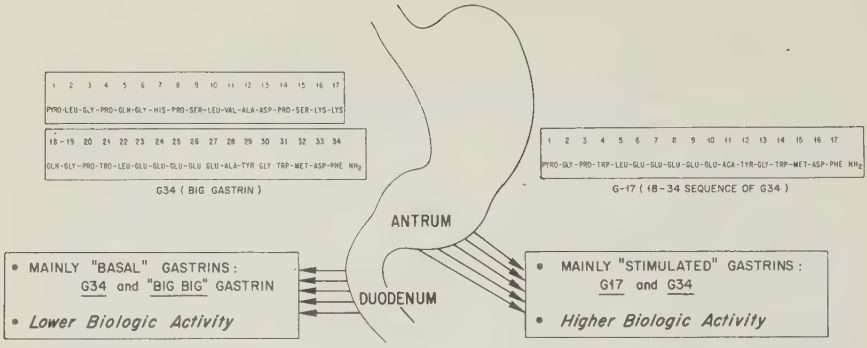
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
PYRO-LEU-GLY-PRO-GLN-GLY-HIS-PRO-SER-LEU-VAL-ALA-ASP-PRO-SER-LYS-LYS
18-19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
GLN-GLY-PRO-TRP-LEU-GLU-GLU-GLU-GLU GLU-ALA-TYR GLY TRP-MET-ASP-PHE NH2
G34 (BIG GASTRIN)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
PYRO-GLY-PRO-TRP-LEU-GLU-GLU-GLU-GLU-GLU-ACA-TYR-GLY-TRP-MET-ASP-PHE NH2
G-17 (18-34 SEQUENCE OF G34)
ANTRUM
DUODENUM
• MAINLY "BASAL" GASTRINS : G34 and "BIG BIG" GASTRIN
• Lower Biologic Activity
• MAINLY "STIMULATED" GASTRINS : G17 and G34
• Higher Biologic Activity

Figure 1. Molecular species of gastrin as related to site of anatomic production or storage. G17 of higher biologic activity is produced mainly from the antrum and is generally released in response to stimulation such as antral distention, food, and vagal stimulation. G34, "big gastrin," generally comprises most of the basal circulating levels of gastrin, has a lower biologic activity, and arises from both the antrum and the duodenum, perhaps more from the duodenum. This concept of the molecular species of gastrin is not universally accepted, and some authors may differ.

Tracy[57] from a very large gastrinoma, G13 is the C terminal tridecapeptide fragment of the bigger forms of gastrin. The nonsulfated forms usually predominate in all three human gastrins in the proportion of 2:1.[58]

When Yalow and Berson[152] treated big gastrin with trypsin, an equivalent amount of little gastrin appeared in the serum sample. They predicted that the trypsin sensitive region of gastrin must be composed of two consecutive basic amino acids. This was confirmed by Gregory and Tracy,[58] who found that the liberation of the "tryptic" G17 from G34 occurred together with free lysine.

Other forms of gastrin exist, such as the "big-big" gastrin of Yalow and Berson, which is believed to have a much larger molecular weight than G34, and component I of Rehfeld, Stadil, and Vikelsoe.[111] Both await chemical and biologic characterizations.

Significance of Gastrin Heterogeneity

The heterogeneity of molecular forms of gastrin affects its catabolism, its "in vivo" manufacture, and the effect of various stimulatory agents on its release. The half-life of G17, G34, and big-big gastrin, as determined in the dog, has been reported as 3,9 and 90 minutes respectively,[124] an observation which could explain why bigger gastrin molecules predominate in determinations of basal serum gastrin.

Stimulation of the gastrin producing cells also affects the serum concentration of its various components. G17 was found to constitute the largest serum gastrin peak following the stimulation of the dog's antral mucosa.[129, 154] In contrast, antral acidification suppresses G17 and G34 but not "big-big" gastrin. In fasting human serum, big gastrin and big-big gastrin also predominate,[108, 151, 154] while stimulation leads to increased proportions of G34, G17, and mini gastrin.[121, 135] Of added significance, G17 is a more biologically active molecule than big gastrin.[26,

[136] In one study, it was shown that although G17 made up only 30 per cent of serum gastrin, it accounted for 70 per cent of its acid stimulatory activity.[32]

GASTRIN PRODUCTION

Site of Gastrin Production

Human gastrin is produced in both the antrum and duodenum by the G cells. These are specialized endocrine cells which fit the cytochemical and ultrastructural characteristics of the APUD cell series (for Amine Precursor Uptake and Decarboxylation). The APUD concept has been developed by Professor Pearse in London, and postulates that such cells originate from the neuroectoderm and migrate to the developing gut.[102] Although agreement with this concept is not universal, the hypothesis is supported by cytochemical findings[102, 118] and may be helpful in a better understanding of the mechanism of the hormonal release of the gut hormones. Structurally, the cells are characterized by a narrow apex and a wide basal region packed with dense granules. They have microvilli on the lumenal (or narrow) side; these may subserve a sensory function in response to chemical changes in the lumenal contents.[22]

Much of the human serum gastrin is produced by the antral mucosa where G17 constitutes more than 90 per cent of the extracted gastrin,[7, 21, 112] whereas the duodenal mucosa has an estimated 10 to 33 per cent of the antral concentration of gastrin which consists mainly of big gastrin.[7, 112] The pancreatic islets contain only minimal amounts of immunoreactive gastrin,[22] perhaps too small to serve any physiologic function.[110]

Mechanism of Gastrin Release

The natural (physiologic) stimulus for gastrin release is by food. This is achieved by three main mechanisms. First, direct action on the G cells which is considerably affected by the chemical nature of foods. Thus, polypeptides resulting from light peptic digestion of proteins are effective releasers of gastrin in the dog; whole protein molecules, such as albumin, do not share this ability.[24] Gastrin is also released by alcohol and by amino acids.[41] In man, high protein meals, casilan (milk protein derivative), and the amino acid glycine were the most potent releasers of gastrin, whereas pure fat and carbohydrates were poor releasers. Unlike what is observed in the dog, alcohol was found to be a poor stimulant of gastrin.[77]

The second mechanism is by mechanical distention of the antrum[25] or fundus.[27] This has been shown experimentally to result in the release of gastrin and hence to acid secretion.[24] The effect of mechanical distention on gastrin release is probably mediated by local reflexes and can be blocked by atropine.[138] In the innervated stomach, however, acid release is also affected by the "pyloro oxyntic reflex."[25] The importance of mechanical distention is that chemical stimulants seem to require such a background for maximal effectiveness.[24]

The third mechanism is through vagal stimulation: sham feeding has been shown to cause the release of gastrin both in the dog[25] and in patients[74] with duodenal ulcer, thus allowing gastrin to participate in the total acid secretory response of sham feeding. However, sham feeding was not followed by gastrin release in healthy individuals.[95]

Species variation is clearly exemplified in the dog, where Olbe[100] has shown that sham feeding, measured by the acid secretion from a Pavlov pouch, was enhanced by subthreshold amounts of gastrin[99] and markedly diminished by antrectomy. This contribution, however, does not seem to be a major one in man, as the direct vagal stimulation of the oxyntic population has been shown to be the major mechanism of acid secretion in sham feeding.[13, 83]

To explain the discrepancy, Olbe[101] has postulated the presence of an "inhibitor" (possibly "vagal dependent") that is most effective in healthy men, but only moderately so in patients with duodenal ulcer, and least effective in the dog. However, this proposition remains entirely speculative.

More about the role of the vagus on gastrin release has been learned by observing the effect of vagotomies in their different forms of gastrin release. In one study,[47] fasting PG increased significantly following selective and parietal cell vagotomies, presumably as a result of the lack of acid inhibition that follows both operations, whereas meat extract stimulation augmented the release of PG only when the antrum's innervation was kept intact by the purely "parietal cell" vagotomy.

A still unexplained feature of vagal release of gastrin in man is that instead of being blocked by atropine as seen in the dog,[6] stimulated gastrin release is enhanced by atropine.[44] Given a cholinergic basis for the vagal release of gastrin, this could just reflect a resistance to the atropine "block."[117]

Gastrin release may be affected by other stimuli. Acetylcholine is a powerful releaser of gastrin when applied to the antral mucosa,[116] as well as to the duodenal mucosa.[144] Ingested calcium releases endogenous gastrin[82] and could thus contribute to the postprandial release of the hormone. Calcium, also a powerful blood-borne stimulus, correlates significantly with gastrin release in hyperparathyroidism,[29, 143] although it is not clear what role calcium has in the release of gastrin in healthy individuals. Epinephrine is another such stimulus which releases gastrin,[64] an effect which is blocked by α-blockers in pheochromocytoma patients, and by β-blockers in normal individuals.[129]

Regulation of Gastrin Release

Gastrin release is inhibited by the very acidity it stimulated.[141] *Antral* acidification is perhaps the most powerful inhibitor of gastrin release both in the dog[23] and in man.[16]

It is of major clinical importance in patients whose acid secretory response is either diminished or abolished. In the gastritis that results from the presence of parietal cell antibodies,[61] the lack of a physiologic feedback mechanism is presumably responsible for the gradual increase of the G cell population with age. Hypergastrinemia has also been shown to occur with pernicious anemia,[90] presumably for the same

reason. It is also a feature of the retained excluded alkaline bathed antrum sometimes seen following Billroth II type of gastrectomy.[69, 79]

Bulbar acidification has also been shown to inhibit gastric acid secretion, but his is not achieved through a reduction of serum gastrin.[98]

Hormonal regulation is the second principal mechanism regulating gastrin release. The four peptides of the secretin family (secretin, glucagon, GIP, and VIP) have been shown to inhibit stimulated release of gastrin.[35, 53, 114, 133] VIP acquires an added clinical significance in that context, because of its association with the WDHA syndrome in which watery diarrhea, hypokalemia, and either hypo- or achlorhydria are the major symptoms.[9, 115] Still another hormone that inhbits gastrin release is calcitonin,[42] which seems to have a regulatory function in the release, and possibly the catabolism of gastrin.[5]

PHYSIOLOGIC ROLE OF GASTRIN

Although gastrin is known to have quite a wide spectrum of pharmacologic actions on the intestinal tract,[51, 60, 85] there is less certainty about the physiologic nature of such actions. No doubt exists, however, about the importance of gastrin stimulation of the acid-secreting parietal cells. The stimulation of acid secretion is achieved through a more intricate mechanism than was previously suspected.[6, 85] This involves a complex interaction on the three major receptors of the parietal cells; namely, those of gastrin, acetylcholine, and histamine in such a way that blockade of the acetylcholine receptor (by atropine)[76] or the histamine receptor (by metiamide)[50] or other antagonists, also blocks the action of gastrin on the parietal cell receptor. The clinical importance of this observation is appreciated by observing the effectiveness of selective vagotomy in reducing acid secretion in spite of the accompanying 2- to 3-fold increase of gastrin release.[6, 47]

Although injected or endogenous gastrin will "result" in the stimulation of pepsin secretion,[60] this apparent stimulation of pepsin secretion seems to be secondary to the resulting acidity.[71]

Whereas the physiologic importance of gastrin in the regulation of gastric acid secretion is soundly established, it is not always clear whether its other effects have a physiologic or clinical importance. Nonetheless, it is reasonable to consider physiologic any gastrin effect obtained at the minimal dose needed to stimulate acid secretion. Alternatively, the peak gastrin response in a postprandial situation could similarly be used as a guide. Only pepsin secretion and the stimulation of gastric mucosal blood flow seem to satisfy these criteria.[138] The biologic potentials of gastrin include actions[51, 59, 60, 70, 85] such as the stimulation of water and electrolyte secretion from the stomach, pancreas, liver, and small intestines, increased visceral blood flow, trophic actions, stimulation of the lower esophageal sphincter and stomach, relaxation of the pyloric sphincter, and the release of other hormones such as insulin[109] and calcitonin,[15, 18] as well as VIP.* It is difficult to accept, therefore, that

*Unpublished observation from this laboratory.

gastrin's physiologic role is confined to two or three functions. The study of gastrin on the lower esophageal sphincter (LES) is such an example. Gastrin has been known to stimulate LES.[17, 85] This has been regarded by some as physiologic[17, 88] and has been denied by a number of other investigators.[33, 52, 149] One point remains certain in that context, and this is the rarity of reflux esophagitis in the ZE syndrome.[65] This, however, could be attributed to a trophic effect of gastrin on the physiologic sphincter.[72, 73]

The clinical studies of hypergastrinemia syndrome are, in fact, extremely useful in the study of gastrin's effect in man. Among the effects of gastrin that are seen in the ZE syndrome are the following: parietal cell hyperplasia,[96] increased pancreatic secretion with increased basal and stimulated volume and bicarbonate output[35, 103] and diarrhea which could result from a direct action of gastrin on intestinal water and electrolyte transport inhibition or secretion,[56] but which is more likely the result of steatorrhea in the ZE patients,[130] suggesting that increased circulating levels of gastrin result in these physiologic activities.

Metabolism

Gastrin catabolism is somewhat dependent on the size of the molecule. In one report, the half-life of infused G17 and G34 was measured in dogs and found to be 3 and 15 minutes respectively.[136] A consensus is that the larger forms of gastrin are less readily metabolized than the smaller and biologically more active molecules, and thus have a longer half-life.

The kidneys seem to assume the major role in the breakdown of gastrin,[63] a fact which readily explains the state of hypergastrinemia in renal failure[30, 143] and could account for the upper gastrointestinal ulceration and bleeding in uremic patients.[143] The small intestines also seem to have a role in gastrin metabolism,[123, 146] but jejunoileal bypass does not result in hypergastrinemia.[20] The role of the liver in gastrin metabolism is still unsettled. In a recent study on humans,[28] no significant difference was found between gastrin concentrations measured in the umbilical vein and the antecubital vein. In a study in dogs, there was a significant alteration in the stimulated endogenous gastrin as a result of its passage through the liver, resulting in the formation of big gastrin molecules (? from G17), as well as in the deamination of the stimulated little (G17) gastrin.[2] These results, however, differed from those of Thompson and his co-workers.[106, 127] The lung apparently has little effect in catabolism of gastrin.[31]

Hypergastrinemia

Increased concentrations of circulating gastrin are found in a number of clinical situations. There are three main causes: First, increased production as seen in the ZE syndrome; second, decreased breakdown as in renal failure; and third, lack of acid inhibition as seen in parietal cell atrophy (Fig. 2).

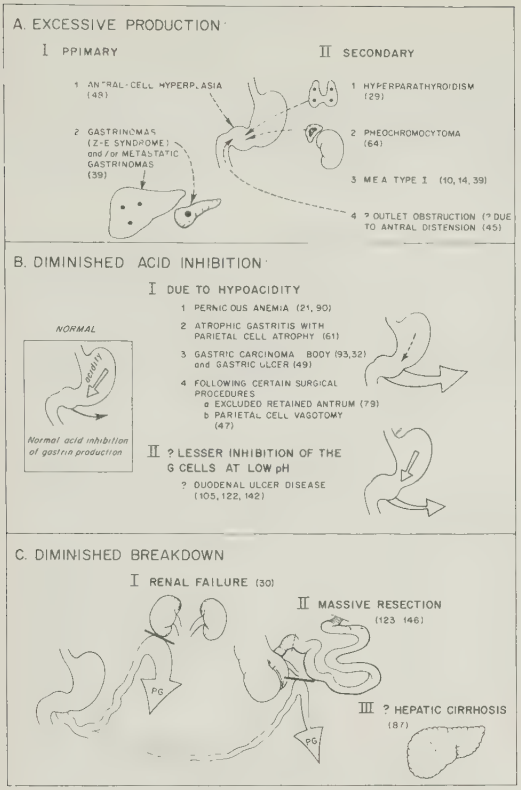
A. EXCESSIVE PRODUCTION
I PPIMARY
II SECONDARY
1 ANTRAL-CELL HYPERPLASIA (48)
2 GASTRINOMAS (Z-E SYNDROME) and/or METASTATIC GASTRINOMAS (39)
1 HYPERPARATHYROIDISM (29)
2 PHEOCHROMOCYTOMA (64)
3 MEA TYPE I (10, 14, 39)
4 ? OUTLET OBSTRUCTION (? DUE TO ANTRAL DISTENSION (45)
B. DIMINISHED ACID INHIBITION
I DUE TO HYPOACIDITY
1 PERNICIOUS ANEMIA (21, 90)
2 ATROPHIC GASTRITIS WITH PARIETAL CELL ATROPHY (61)
3 GASTRIC CARCINOMA BODY (93,32) and GASTRIC ULCER (49)
4 FOLLOWING CERTAIN SURGICAL PROCEDURES
a EXCLUDED RETAINED ANTRUM (79)
b PARIETAL CELL VAGOTOMY (47)
NORMAL
acidity
Normal acid inhibition of gastrin production
II ? LESSER INHIBITION OF THE G CELLS AT LOW pH
? DUODENAL ULCER DISEASE (105, 122, 142)
C. DIMINISHED BREAKDOWN
I RENAL FAILURE (30)
II MASSIVE RESECTION (123 146)
III ? HEPATIC CIRRHOSIS (87)
PG
PG

Figure 2. A pictorial representation of hypergastrinemia based on increased production, decreased catabolism and perhaps other less well understood factors.

Gastrin and Ulcer Disease

Hypergastrinemia concerns the surgeon mainly as a result of the ulcer involvement in therapy of disease. Awareness of the therapeutic manuevers necessary in the treatment of hypergastrinemia may spell the difference between mortality and survival, as in the following.

The Zollinger-Ellison Syndrome (Gastrinoma)

The syndrome was first described by Zollinger and Ellison in 1955[155] who suggested that the responsible secretaguogue was glucagon. The responsible secretaguogue was definitely characterized as gastrin by Gregory, et al. in 1967,[55] although earlier work suggested it.[54] It consists of the following features,[10, 39, 40, 67, 147-155] although not all are invariably present:

1. Fulminant or recurrent ulcer disease, often in typical locations
2. Massive hypersecretion of gastric acid
3. Diarrhea
4. Hypergastrinemia
5. A non-β islet cell tumor of the pancreas (the ZE tumor or gastrinoma). This is occasionally found in the wall of the duodenum or stomach, and rarely in extragastrointestinal locations.

The importance of the ZE syndrome lies in its seriousness. When untreated the mortality has been reported to be 78 per cent,[40] while a reported 30 per cent of the diagnoses are still made in the autopsy room.[4] Of nearly 1000 cases collected by Wilson,[147] 59 per cent of the tumors were malignant. Although malignancy is a problem with late survival, early mortality is more often the result of excessive gastrin release, which has the following devastating effects:

1. An increasing rate of gastrin secretion that results from climbing H^+ and Cl concentrations, and gives rise to an almost pure HCl with maximal secretion.[92] In one study, ten ZE patients had a mean basal acid secretion of 44.3 mEq per hr compared with 2.3 mEq per L in normals.[37] The above changes are also accompanied by a reciprocal decrease in Na^+ and an increase in K^+ secretions.[92]

2. The wide spectrum of actions of gastrin is evident in gastrinoma patients in whom both basal and secretin stimulated pancreatic secretion are elevated as regards volume and bicarbonate secretions.[37]

Concomitantly, gastrin could also interfere with intestinal water and Na^+ absorption[56] as well as be responsible for the steatorrhea[130] perhaps associated with lack of activation of pancreatic lipase by acidified chyme. All features of the disease need not be present in each patient. Diarrhea may be the only symptom,[39] but is absent in 30 per cent[39] to 70 per cent of the cases.[10] Some patients lack the massive acid hypersecretion.[148] Occasionally, plasma gastrin is not elevated,[128, 139] despite repeated determinations. Finally, some patients with the classic features of the syndrome have diffuse hyperplasia of the islets, but no tumor.[67]

The syndrome often has an insidious onset[39] which adds to the difficulty in diagnosis. Not uncommonly, ZE exists with other endocrine anomalies as part of the multiple endocrine adenomatasis—M.E.A. type I,[10, 14, 39] in which hyperparathyroidism is the most common association.[3, 29] Associated endocrine adenomas in the type I M.E.A. syndrome include, along with the pancreas, the pituitary and adrenal glands.[10, 39, 94]

Zollinger and Ellison[155] realized more than 20 years ago that adequate treatment of the syndrome requires total gastrectomy, and this remains equally true today. It is only in exceptional circumstances that a solitary nonmetastasizing responsible adenoma is found,[34, 155] and the rationale of removing the target organ is, therefore, obvious as most of the mortality results from ulcer disease per se (i.e., acid secretion). Removal of the acid secreting stomach also removes the main cause for secretin release (acid in the duodenum). Secretin is a known releaser of gastrin from gastrinomas,[12] and this may cause a vicious cycle.

Ulcer Disease Secondary to Antral Hyperplasia

A group of patients having the clinical features of ZE but no tumor or islet cell hyperplasia was reported by Polak et al.,[48, 104] who considered the clinical entity they have described as a variant of the ZE syndrome; however, plasma gastrin was significantly lower than in the classical ZE cases. Most important, plasma gastrin concentrations rise with antral stimulation, a response which is not usually seen with gastrinomas. The distinction between the two conditions is categorically made after exam-

ination of the antral G cells by specific immunofluorescence,[48] which shows the increased number of G cells responsible for the condition. Preoperative diagnosis is essential in planning the treatment which should be no less than a total gastrectomy with gastrinomas, whereas a more conservative approach is acceptable with G cell hyperplasia.[48, 62] Not all agree to the existence of this variant, and many would argue for these patients as an extreme example of duodenal ulcer disease.[113]

GASTRIN AND GASTRODUODENAL ULCERS

Although reports differ, no clear relationship has been shown between the high acid secretion in duodenal ulcers (DU) and basal plasma gastrin (PG) concentrations.[142] In a recent report from this laboratory, mean PG in DU was insignificantly higher than in 30 control patients.[142, 145] In gastric ulcer patients, however, most PG is significantly higher than in the control population.[49] On the other hand, PG concentrations in patients with DU have been controversial to say the least; PG being reported as higher,[105, 122] lower,[78] or normal.[48, 119, 132] The discrepancy could, as previously pointed out,[142] stem from the use of different antisera, even by the same laboratory. These discrepancies could also be resolved if the duodenum is the major contributor of basal gastrin,[142] whereas stimulated gastrin is likely of antral origin.[129, 135] McGuigan suggested a relationship between acid secretion and basal gastrin, but we could not confirm any relationship between PG and BAO or PG and MAO.[142]

Much recent attention has focused, therefore, on the concept of greater autonomy in gastrin secretion in patients with DU. The lack of inverse correlation between basal plasma gastrin and basal acid secretion could be argued as evidence for antral escape from its most powerful inhibitor, antral acidification.[142] Most basal gastrin, however, is likely duodenal in origin.[108, 151, 154]

Others have argued for greater release of gastrin to given stimuli in patients with DU. Reeder et al.[107] demonstrated higher serum gastrin concentrations in patients with DU than in controls following calcium infusions. However, serum calcium rose higher in the DU patients, and since release of gastrin by calcium is a threshold phenomenon,[29] the increased release of gastrin seems more likely due to calcium than any characteristic of gastrin release in patients with DU.

Others have suggested "autonomy" of gastrin release following food stimulation.[142] Whatever the cause for this "autonomy," if it exists it does not seem to result from either a greater number of G cells,[48] or a higher concentration of IR gastrin,[86] at least as seen in the ordinary DU patient. This leaves us with two explanations:

1. A defect in the feedback inhibition of gastrin release,[49, 137] possibly the result of a lesser sensitivity of the G cells, to low pH in DU patients. Others[101] have suggested a decrease in a hypothetical inhibitor.
2. A higher sensitivity of the parietal cells of DU patients to the stimulatory effect of gastrin. This has been confirmed in one study with pentagastrin in such patients.[68]

That gastrin has indeed a role in DU disease is further supported by the increase in parietal cell mass[96] in DU patients. This could be explained by the trophic effect of gastrin; the theory of "work hypertrophy" of these cells is a less likely possibility.[51]

In summary, if gastrin is involved in the pathogenesis of DU, it has been difficult to prove despite intense investigation. The principal usefullness of gastrin determinations seems to be the "ruling out" of the Zollinger-Ellision syndrome, and in case of recurrent ulcer, in which its usefulness is limited.

Diagnosis

The diagnosis of ulcer disease is usually based on conventional investigations which follow a thorough history and physical examination and include an upper gastrointestinal series, acid studies and endoscopy in some cases. Fasting serum gastrin should be determined if there is the slightest suspicion of hypergastrinemia.[34]

SERUM GASTRIN DETERMINATION

A radioimmunoassay technique is used to determine serum gastrin. The technique is easy, specific and sensitive. The availability of commercial kits, thought not always reliable,[81] has widened no doubt the use of the assay. A word of caution concerning radioimmunoassay kits and commercial determination of gastrin appears in order. Although some commercial determinations are accurate, values from laboratories whose quality control may be substandard should be reviewed with suspicion. A value which does not coincide with other patient data should be questioned. We have recently had several patients referred to us with diagnosis of ZE syndrome, with apparently erroneously high values for gastrin. The number of these values seems to be increasing.

Radioimmunoassays are more sensitive (measuring picograms) than bioassay (that can measure nanograms). The tests are simpler and more specific than the bioassays which they have completely replaced. The technique utilized in this laboratory is a modification of that of McGuigan,[89, 91] previously described.[29, 47, 142, 145]

Fasting serum gastrin determinations presently are of value only in the differential diagnosis of ulcer disease and hypergastrinemic states.

First, normal gastrin levels differ according to the laboratory in which it is assayed and should be interpreted in that context. Our normal mean is: 26.8 pg per ml ($\pm$ 22.8). Walsh[134] prefers the use of a median value to avoid averaging very high normal values. This brings our normal median value to 19.

Second, plasma gastrin could be deceptively low in gastrinoma patients.[130] This calls for a repetition of the test, as PG fluctuates greatly with time.[128, 130, 139]

Third, a fasting gastrin determination must be seen in the light of other findings, such as vagotomy, acid studies, etc. Hypergastrinemia complicating achlorhydria or renal failure are easily differentiated by acid studies and renal function determination.

Finally, fasting serum gastrin alone may not be able to differentiate among the ZE syndrome, G cell hyperplasia, or recurrent ulcer disease, especially after vagotomy. In order to separate a number of pathologic entities, a number of gastrin stimulation tests may be helpful.

A meat broth extract test,[48] is quite useful, and may differentiate between antral G cell hyperplasia and routine duodenal ulcer disease, if such a distinction exists. Twenty-five grams of commercial "Oxo" are made up to 400 ml with distilled water at a pH of 6.0 at 37°C and drunk by the patient over 5 minutes. Blood samples are then serially taken over a 90-minute period of gastrin determinations. This showed a significantly higher basal and peak gastrin determination in cases of antral G cell hyperplasia, as compared to the levels found in DU disease with a normal G cell population.[48] The test has an added value in the diagnosis of ZE syndrome where autonomous gastrinomas do not respond to antral stimulation by food challenge,[48, 67] a food response is also seen in most cases following vagotomy.

A calcium infusion challenge is also useful. Four to 5 mg of Ca^{++} per kg per hr is infused, often with an additional 4 mg per kg as calcium gluconate in the first half hour.[107, 126, 130] Peak response is usually observed after 3 hours. A response to calcium challenge is seen in normal persons, DU patients, and gastrinoma patients. Normal persons have a significant acid response, but only a slight rise in serum gastrin. DU patients have a much higher acid response and also have a more significant rise in serum gastrin (see discussion above). In ZE syndrome, the integrated gastrin response is more than double that of DU.[107, 130] Magnesium may be used as an alternative to calcium.[130]

An apparently more specific test is that of secretin stimulation (Fig. 3). This produces no change, a decrease,[130, 135] or a very slight elevation in PG in normal individuals, generally less than 80 pg per ml rise. The slight rise may be the result of impurities in the commercially available secretin. Alternatively, the discrepancy of gastrin response in normal in-

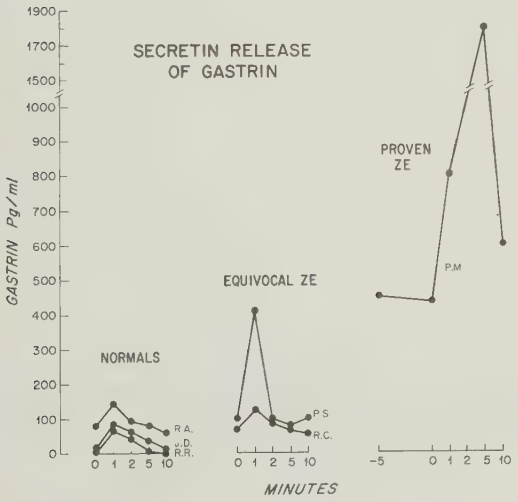

Figure 3. A secretin test on different groups of patients gives varied responses. A response in a normal patient with duodenal ulcer after bolus injection of two units of secretin per kg will lead to less than 80 pg per ml increase in plasma gastrin. Of two patients in whom the diagnosis of Zollinger-Ellison syndrome was equivocal at the time, and who could not be operated on for various medical contraindications, one gave a response of less than 400 pg per ml, but she is still considered a ZE suspect. At the far right, an example of a patient with a proven Zollinger-Ellison syndrome. In general, there is little question concerning the Zollinger-Ellison syndrome, since the response to infused secretin is greater than 400 pg per ml.

dividuals could depend on the molecular form of gastrin released.[125] Secretin, 1 or 2 units per kg, is injected intravenously "as a bolus." Fasting blood samples are collected 5 minutes before the test, at zero time, and then at 1,3,5, and 10 minutes. A doubling or near doubling of the basal values of PG are usually, but not always observed in ZE patients.[66, 69, 123] The secretin infusion test is thought about 90 per cent accurate for patients who increase basal values by more than 50 per cent.[123] Hypergastrinemia accompanying recurrent ulcers with a retained excluded antrum generally respond to the secretin test with a decreased PG.[69, 79] A similar depression has been observed in antral G cell hyperplasia.[69, 79]

Other tests for gastrin release have been used, and may be helpful.

The applicability of the Hollander Test[34] for the release of gastrin is one example. Gastrin release by insulin is observed only with intact antral innervation[80] as seen with parietal cell vagotomy, while selective vagotomy that denervates the antrum abolishes that effect. Arginine infusion has also been shown to release gastrin only with an intact and innervated antrum.[134] A recent study on antacid has revealed that the nonbuffering chloride compounds—$MgCl_2$, $AlCl_3$, and $CaCl_2$—result in a higher gastrin response in DU than in normal controls[46] in spite of a pH of 2. Whether these tests will acquire diagnostic value remains to be seen.

In patients with the type of atrophic gastritis that follows parietal cell atrophy, high gastrin levels are suppressed by antral acidification.[61] The same results are obtained with secretin in such cases,[61] and the presence of parietal cell antibodies will secure the diagnosis, otherwise antral acidification is of little value in the diagnosis of ulcer disease.[16]

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Gastric Secretion and Motility in Duodenal Ulcer: Effect of Current Vagotomies

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Three types of vagotomy are currently being employed in the surgical treatment of chronic duodenal ulcer. *Proximal* gastric vagotomy (highly selective vagotomy, parietal cell vagotomy) vagally denervates the fundus and corpus of the stomach but leaves intact the vagal innervation of the antrum and other abdominal viscera. *Total* gastric vagotomy (selective vagotomy) vagally denervates the entire stomach but not the other abdominal viscera. *Truncal* vagotomy vagally denervates the entire stomach and all other abdominal viscera receiving vagal innervation.[12]

Our objective in this article is to contrast the effects of the three vagotomies on gastric secretion and motility in duodenal ulcer.

VAGAL REGULATION IN HEALTH

The vagi have an important role in regulating gastric secretion and motility in health.

Gastric Secretion

STIMULATION. The oxyntic cells are stimulated to secrete hydrochloric acid by acetylcholine, which is released by the vagi, as well as by histamine and gastrin. These chemical regulators have been called "first messengers." Each binds to a specific receptor on the wall of the oxyntic cell. This union initiates the formation of a "second messenger" within the cell which activates the intracellular secretory mechanism.

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Cyclic guanosine 3′.5′-monophosphate (cyclic GMP) appears to be the second messenger activated by acetylcholine in the oxyntic cell in some animals. Cholinergic stimuli increase the formation of cyclic GMP in canine fundic mucosa, an effect prevented by atropine or vagotomy.[11] In contrast, cyclic adenosine 3′,5′-monophosphate (cyclic AMP) is probably the second messenger for histamine in dogs,[10] rodents, and amphibians.[23] Histamine, but not cholinergic agents or gastrin, stimulates the formation of cyclic AMP in canine fundic mucosa, an effect blocked by metiamide, a histamine H_2-blocking agent. The second messenger or messengers present in human oxyntic cells are unknown.

Only small amounts of acid are secreted during fasting in healthy subjects (2 mEq per h). But the thought, smell, taste, chewing, and swallowing of appetizing food bring about an increase in the rate of secretion, a phenomenon called the "cephalic phase" of gastric secretion. These stimuli initiate vagal reflexes that result in the release of acetylcholine both in the fundic mucosa and in the antral mucosa. The acetylcholine released in the fundic mucosa acts directly on the oxyntic cells to increase their production of acid. The acetylcholine released in the antrum stimulates the secretion of acid indirectly by causing antral "G" cells to discharge gastrin, which in turn stimulates the oxyntic cells. The magnitude of the response when both fundic and antral pathways are acting exceeds that for either pathway alone. However, the direct effect of acetylcholine on the oxyntic cell appears to predominate in man, since the secretion of acid in response to sham feeding is abolished by proximal gastric vagotomy but not by antrectomy.[24, 25]

The entrance of food into the stomach initiates the second phase of gastric secretion, the gastric phase. Distention of the fundus and corpus by food activates both long (vagovagal) and short (intramural) reflexes that cause the secretion of acid (oxynto-oxyntic reflexes).[14] Distention of the nonacidified antrum causes the release of antral gastrin (pyloropyloric reflex), which then stimulates secretion. However, distending the antrum with an acidic solution does not increase the release of gastrin and so does not stimulate the secretion of acid from a vagally denervated canine fundic pouch (gastrin-dependent mechanism), but it does stimulate secretion from a vagally innervated fundic pouch (gastrin-independent pyloro-oxyntic reflex).[8] Vagal denervation of the antrum destroys the gastrin-independent reflex. Conversely, distention of the oxyntic area causes gastrin to be released from a nondistended, nonacidified antrum (oxyntopyloric reflex).[9] Acidifying the antrum suppresses the release of gastrin caused by proximal gastric distention and greatly diminishes, but does not eliminate, the secretion of acid from the oxyntic area.

The contact of food with gastric mucosa also stimulates the secretion of acid. Bathing the oxyntic area with polypeptides and amino acids induces the secretion of acid by a gastrin-independent mechanism that is only minimally inhibited by atropine and metiamide.[7] Bathing the antral mucosa with the same dietary components releases gastrin, which in turn stimulates the secretion of acid.[14]

Finally, the entrance of chyme into the small intestine stimulates a third phase of gastric secretion, the intestinal phase. This phase may be

mediated by intestinal gastrin, "entero-oxyntin," and other stimulatory humoral substances.

Probably all phases of gastric secretion have both neural and humoral components. In addition, the three principal chemical regulators—acetylcholine, gastrin, and histamine—also influence each other's action. Atropine (or vagotomy) and histamine H_2-blockers inhibit the oxyntic response to all three stimulants.

Inhibition. The secretion of acid can be decreased either by withdrawing stimulation or by enhancing inhibition of the oxyntic cells, and the vagi have a role in both phenomena. Stimulation by gastrin can be diminished by acidification of the antrum, which decreases formation or release (or both) of the hormone.[34] There may also be vagal fibers in the antrum that inhibit the release of gastrin. Electric stimulation of antral vagal nerves has been shown to inhibit the secretion of acid, while cutting the same nerves increases the secretion.[19] The release of antral gastrin in response to insulin hypoglycemia can be enhanced by selectively blocking vagal inhibitory fibers to the antrum.[3]

The secretion of acid is also diminished by humoral inhibitors from the small intestine. Inhibitory hormones are secreted in response to the entrance of fat, acid, or hyperosmolar substances into the small bowel. The exact nature of the inhibitors is unknown. Candidates include secretin, cholecystokinin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP), and glucagon.[30]

The vagal nerves modify intestinal inhibitory pathways. Fat or acid placed in the human duodenum no longer inhibits acid secretion after vagotomy.[20, 32] Increased postprandial secretion of acid occurs after truncal vagotomy or extragastric vagotomy in antrectomized dogs with vagally denervated fundic pouches; this suggests that the release of an inhibitor from the small intestine is under vagal influence.[22]

Gastric Motility

The vagi have a unique role in regulating the motility of both the proximal and the distal parts of the stomach, in keeping with the different motor functions of these two gastric regions.[4]

Proximal Stomach. The proximal part of the stomach acts as the gastric reservoir, receiving and storing ingested food. Its slow, sustained contractions exert a steady pressure on the gastric content, gradually pressing the content toward the distal stomach and the duodenum.

The rate of emptying of gastric content depends on the difference in pressure between the stomach and the duodenum, and it also varies with the resistance to the flow of chyme.[27] Because the sustained contractions of the proximal stomach are the main determinant of pressure in the stomach, they have a major influence on gastric emptying.

Some vagal neurons stimulate proximal gastric contractions, whereas others inhibit them, as do sympathetic neurons.[1] The transmitter released by the vagal stimulatory neurons is acetylcholine, which depolarizes smooth muscle cells and results in action potentials and contractions. The transmitter released by the vagal inhibitory neurons and its mode of action are unknown. Adenosine triphosphate and dopamine are candidates.

Two properties of the proximal stomach are especially important in

the control of intragastric pressure and gastric emptying: receptive relaxation and accommodation to distention. Both are regulated by vagal nerves.

As boluses of ingesta pass through the esophagus into the stomach, the proximal stomach relaxes to receive them, a phenomenon called "receptive relaxation."[4] Intragastric pressure actually decreases before the arrival of the bolus, and it remains low during repeated swallowing. After swallowing, intragastric pressure returns toward the control level. Receptive relaxation is mediated by vagal inhibitory fibers that are reflexly activated.

The proximal stomach also has the remarkable ability to adapt to increasing volumes with little change in intragastric pressure. Intragastric pressure increases to about 10 cm of water as the stomach is gradually distended to 300 to 500 ml, but with continued distention to 800 to 1000 ml, little further increase in pressure occurs.[4] Accommodation is also mediated in part by vagal neurons. Receptors in the wall of the stomach sensitive to stretch and pressure activate vagal afferent neurons; these synapse with neurons in the central nervous system which in turn activate vagal inhibitory fibers.

The maintenance of low intragastric pressure with gastric filling, as made possible by receptive relaxation and accommodation and the vagal nerves, means that the gastroduodenal gradient in pressure is kept small during eating and that gastric emptying is not hurried.

The vagi also facilitate hormonal regulation of proximal gastric motility. For example, gastrin inhibits proximal gastric contractions, decreases intragastric pressure, and slows gastric emptying.[35] The vagi enhance this effect, for after vagotomy the sensitivity of the smooth muscle in the proximal stomach to gastrin is diminished.[28]

The vagi may also modify responses to cholecystokinin, secretin, glucagon, and motilin, all of which slow gastric emptying, but appropriate testing has not yet been done.

THE DISTAL STOMACH. The distal part of the stomach acts as the gastric mixer and grinder.[4] Its peristaltic contractions blend the gastric content with gastric juice and thoroughly triturate gastric solids before allowing them to pass into the duodenum.

A gastric pacemaker in the orad corpus sets the pace of gastric peristalsis and determines the velocity and direction of its propagation.[33] The pacemaker generates regularly a cyclic change in potential, called the pacesetter potential, which propagates aborally from the orad corpus to the pylorus. The pacesetter potential partially depolarizes the gastric smooth muscle as it sweeps distally, bringing the muscle cells closer to the threshold for contraction. The threshold is reached when additional stimuli, such as acetylcholine or gastrin, act on the muscle to complete its depolarization. Contractions then occur, and they occur at a frequency of 3 per min, the frequency of the pacemaker and its pacesetter potential.

The pacemaker and the pattern of pacesetter potentials are myogenic phenomena, but the vagal nerves stabilize the rhythm of the pacemaker and prevent ectopic pacemakers from disturbing the regular pattern of pacesetter potentials in the distal stomach.

As in the proximal stomach, vagal nerves augment and sympathetic nerves inhibit contractions in the distal stomach. The more vagal stimulatory nerves that fire, the more acetylcholine is released, and the stronger are the peristaltic contractions that result. The existence of vagal inhibitory motor nerves in the distal stomach has not been shown.

The influence of the vagi in modifying hormonal responses in the distal stomach is unknown. Gastrin increases the frequency of the gastric pacemaker and stimulates peristalsis, in marked contrast to its inhibitory effect in the proximal stomach. Cholecystokinin and motilin also stimulate distal gastric contractions, whereas secretin, glucagon, VIP, GIP, and bulbogastrone inhibit peristalsis.

VAGAL REGULATION IN DUODENAL ULCER

An attractive hypothesis is that increased vagal "drive" results in changes in gastric secretion and motility that lead to duodenal ulcer.

Gastric Secretion

The secretion of acid during fasting is greater in patients with duodenal ulcer than in normal subjects, but there is much overlap in the range of values of the two groups. The hypersecretion in duodenal ulcer is due to several factors. Subjects with ulcer have twice as many oxyntic cells as do nonulcer subjects (ulcer, 2 billion; nonulcer, 1 billion), and this contributes to their increased capacity to secrete acid.[17] The dose of stimulant necessary to produce half-maximal secretion of acid is smaller in ulcer patients than in control patients, a reflection of increased responsiveness of the oxyntic cells in ulcer.[17] Patients with ulcer release more gastrin than do normal subjects when fed a meal of protein; this shows that there is increased strength of stimulation in duodenal ulcer.[31] Lastly, the suppression of the release of gastrin by antral acidification is less in ulcer patients than in controls, an indication that there is impaired inhibition of secretion in ulcer.[31]

Gastric Motility

Gastric accommodation to distention is not altered in duodenal ulcer,[18] nor are there changes in the rhythm or frequency of the gastric pacemaker and gastric peristalsis.[26] However, peristaltic contractions are stronger in patients with duodenal ulcer than in healthy subjects,[16] and gastric emptying of food is more rapid.[29] The rapid entrance of acidified chyme into the duodenum contributes to the inability of the duodenum to neutralize the acid, leading to ulceration.

EFFECT OF VAGOTOMY

Gastric Secretion

Proximal Gastric Vagotomy. Vagal denervation of the gastric fundus and corpus immediately reduces basal acid output (BAO) by 75 to 80 per cent and peak acid output (PAO) in response to pentagastrin or

Table 1. *Gastric Secretion of Acid After Vagotomy**

	VAGOTOMY		
	TV	TGV	PGV
No. of patients	704	140	191
BAO (per cent reduction)	74	64	81
PAO (per cent reduction)	66	62	58

*TV = truncal vagotomy; TGV = total gastric vagotomy; PGV = proximal gastric vagotomy; BAO = basal acid output; PAO = peak acid output in response to pentagastrin or histamine. Data are collected from the literature.

meat extracts by 55 to 70 per cent (Table 1).[6, 19] The PAO in response to insulin also decreases. In one report, PAO after insulin decreased from 33 mEq per h preoperatively to 0.5 mEq per h 1 week after vagotomy.[21]

The secretion of acid tends to return toward prevagotomy values in the first year after proximal gastric vagotomy, especially the PAO in response to insulin. However, by 5 years after operation, the BAO and PAO after pentagastrin are still reduced by 79 and 48 per cent, respectively (Fig. 1).[13] The PAO in response to insulin also remains remarkably small at 3.5 mEq per h, even though 90 per cent of the insulin tests were positive by Hollander's criteria.

Proximal gastric vagotomy also reduces the secretion of acid that occurs in response to distention of the proximal human stomach,[2] decreases the output of pepsinogen in response to various stimuli,[6] and increases the concentration of gastrin in the serum.[15]

TOTAL GASTRIC AND TRUNCAL VAGOTOMY. Total gastric and truncal vagotomy reduce BAO and PAO in response to histamine, pentagastrin, and meat extracts by 60 to 80 per cent and 50 to 70 per cent, respectively (see Table 1).[19] The magnitude of the reduction in acid secretion is similar to that found after proximal gastric vagotomy, and all three types of vagotomy are followed by the same slight tendency for recovery (see Table 1). Pepsinogen secretion induced by insulin or pentagastrin is

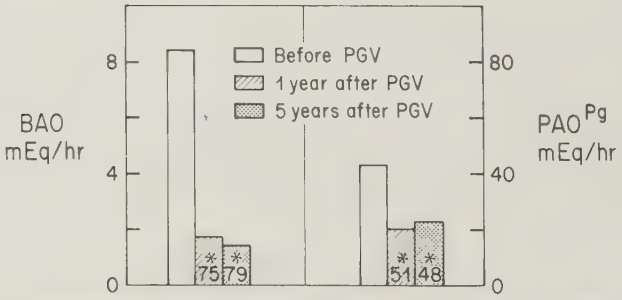

Figure 1. Substantial decreases in basal acid output (BAO) and in pentagastrin-induced peak acid output (PAO^{Pg}) occurred in 21 subjects with duodenal ulcer at 1 and 5 years after proximal gastric vagotomy (PGV). Asterisk indicates per cent reduction in acid output. (Data from Greenall, M. J., Lyndon, P. J., Goligher, J. C., and Johnston, D.: Long term effect of highly selective vagotomy on basal and maximal acid output in man. Gastroenterology, 68:1421, 1975. Used with permission.)

equally diminished by proximal gastric vagotomy and total gastric vagotomy.[6]

The concentrations of gastrin in the serum during fasting and after a meal of protein are greater after each of the three types of vagotomy than before vagotomy. The postvagotomy hypergastrinemia may be attributed to decreased inhibition of release of antral gastrin by acid and to increased liberation of extragastric gastrin. Basal serum gastrin is the same whether the antrum is innervated or not; this suggests that acidity controls basal gastrin levels.[15] The gastrin response to a protein meal is greater after proximal gastric vagotomy than after total gastric vagotomy but less than after truncal vagotomy. However, the secretion of acid after all three vagotomies is similar, and this points out the importance of the decreased responsiveness of the vagally denervated oxyntic cells to gastrin.

Gastric Motility

PROXIMAL GASTRIC VAGOTOMY. Vagal denervation of the proximal stomach impairs receptive relaxation and accommodation to distention. Greater increases in pressure occur with gastric filling after proximal vagotomy compared with before, resulting in early satiety, epigastric fullness, and rapid gastric emptying of liquids[5, 18] (Fig. 2). Fortunately, the acceleration in the rate of gastric emptying produced by proximal gastric vagotomy has seldom been great enough to result in the "dumping syndrome" or diarrhea.[19]

Proximal gastric vagotomy also vagally denervates the orad corporeal gastric pacemaker. The denervation produces some instability of the gastric pacemaker, and periods of antral dysrhythmia secondary to an ectopic pacemaker occasionally occur. Fortunately, these periods are infrequent after the first postoperative week.

Proximal gastric vagotomy preserves the vagal innervation of the antrum and pylorus. Peristalsis and antral mixing and grinding are not

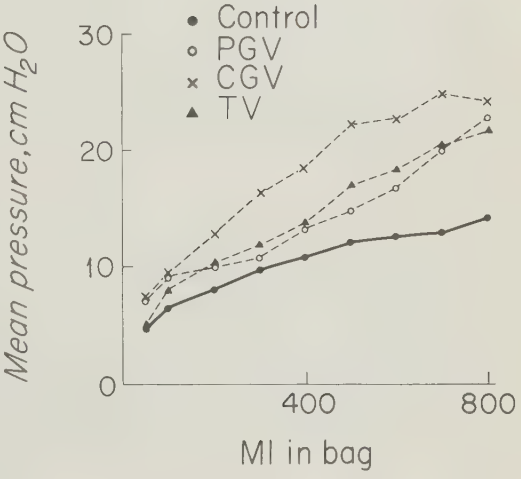

Figure 2. Proximal gastric vagotomy (PGV), complete gastric vagotomy (CGV), and truncal vagotomy (TV) all impair canine gastric accommodation to distention. (Reproduced from Wilbur, B. G., and Kelly, K. A.: Effect of proximal gastric, complete gastric, and truncal vagotomy on canine gastric electric activity, motility, and emptying. Ann. Surg., *178*: 295, 1973. Used with permission.)

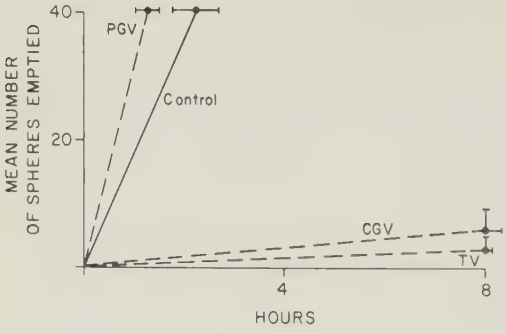

Figure 3. Complete gastric vagotomy (CGV) and truncal vagotomy (TV) slow canine gastric emptying of solids, but proximal gastric vagotomy (PGV) does not. (Modified from Wilbur, B. G., and Kelly, K. A.: Effect of proximal gastric, complete gastric, and truncal vagotomy on canine gastric electric activity, motility, and emptying. Ann. Surg., 178:295, 1973.)

greatly impaired by proximal gastric vagotomy, and gastric emptying of solids is not altered. Operations that facilitate gastric emptying of solids, such as pyloroplasty and gastroenterostomy, are not needed.

TOTAL GASTRIC AND TRUNCAL VAGOTOMY. Total gastric vagotomy (selective vagotomy) and truncal vagotomy vagally denervate the proximal stomach and impair receptive relaxation and gastric accommodation, just as proximal gastric vagotomy does, and result in easy filling and rapid gastric emptying of liquids (see Fig. 2).[5] These operations also vagally denervate the gastric pacemaker and distal stomach, and this disturbs slightly the stability of the gastric pacemaker and the pattern of electrical activity of the distal stomach. But the disturbances are small and they tend to disappear with time, as with proximal gastric vagotomy.

The main difference between total gastric vagotomy or truncal vagotomy and proximal gastric vagotomy is that the more extensive vagotomies vagally denervate the distal stomach, thereby weakening peristalsis, impairing trituration, and slowing gastric emptying of solids, whereas proximal gastric vagotomy does not (Fig. 3). The stasis of solids that results with distal gastric denervation is so severe that operations to decrease the resistance to the passage of solids at the pylorus (pyloroplasty) or bypass the pylorus (gastroenterostomy) are usually required. Unfortunately, in addition to facilitating gastric emptying of solids, pyloroplasty disrupts and gastroenterostomy bypasses the closing mechanism at the pylorus which prevents reflux of duodenal content into the stomach. Increased duodenal-gastric reflux can result and lead to bilious vomiting and alkaline gastritis.[19]

SUMMARY

Proximal gastric vagotomy, total gastric vagotomy, and truncal vagotomy all decrease gastric secretion of acid and pepsinogen, increase the concentration of gastrin in the serum, impair gastric receptive relaxation and accommodation, and speed gastric emptying of liquids. Only proximal gastric vagotomy preserves antral motility, gastric emptying of solids, and the pyloric barrier to duodenal-gastric reflux.

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Gastric Emptying—Physiology and Measurements

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Interest in the physiology and regulation of gastric emptying dates back to 1833 when Beaumont[1] observed that the length of time food remains in the stomach after a meal depends upon the type of food eaten. Although many investigations have detailed factors (pH, osmolarity, and fat) that influence the rate of gastric emptying, the clinical applications of measurement of gastric emptying in man are limited. Operations for duodenal ulcer are followed by alterations in motility and emptying. These are manifest clinically by early satiety, dumping, and diarrhea. Elsewhere in this symposium, Dozois and Kelly analyze preoperative and postoperative neural factors and changes that relate to gastric emptying and motility.

This article briefly reviews other factors that influence gastric emptying and the methods that assess gastric emptying in man.

HISTORY

Early work on gastric emptying was summarized by Marbaix.[46] By 1898 it had been demonstrated that solutions passing through the pylorus into the intestine could delay gastric emptying, particularly when compared to solutions that egressed through a duodenal fistula. Studies also showed that the greater the volume in the stomach, the more rapid the rate of emptying. Distention of the stomach, regardless of the solution causing the distention, resulted in an increased rate of gastric emptying.[32, 54] Marabaix demonstrated that 250 cc of air plus 250 cc of water emptied at the same rate as 500 cc of water.[46] The effects of osmotic pressure on gastric emptying was shown in 1905 by Carnot and Chassevant.[4] Hypertonic and hypotonic solutions delayed gastric emptying.

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NORMAL GASTRIC EMPTYING

Anatomic Factors

Three anatomic areas of the stomach regulate emptying: (1) the proximal stomach (fundus), (2) the distal stomach (antrum), and (3) the pylorus. The division between proximal and distal stomach as defined by Kelly[14] is midway on the lesser curvature and one-third the distance on the greater curvature (as measured from the esophagus). Although this area does not correspond to anatomic subdivision of fundus, corpus, and antrum, it functionally divides the stomach into areas concerned with the emptying of liquids (proximal) and solids (distal stomach) (Fig. 1).

The proximal stomach serves as a reservoir where receptive relaxation occurs. The distal stomach is concerned with antral contractures. A pacemaker located on the orad corpus, greater curvature side of the stomach, is the site of an electrical wave which passes downward to the pylorus. When this electrical wave is associated with an action potential, a coupling phenomenon may result. This is then followed by an antral contracture. Experimentally, only 26 per cent of electrical waves were conducted.[14] The simultaneous distal contractions result in antral systole causing solids to leave the stomach (propulsion) when the pylorus is opened and mixing and grinding (retropulsion) to occur when the pylorus is closed.

Pylorus

Although anatomically demonstrated, the existence of a physiologic pyloric sphincter has created controversy. Fisher and Cohen[20] have shown by manometric studies in 28 humans that a high pressure zone 1.5 cm in length with a resting pressure of 5.3 $\pm$ 0.5 mm Hg is present. They suggested that the pylorus is a physiologic sphincter "that contracted in response to duodenal hormonal stimuli and altered the retrograde movement of duodenal contents into the stomach." Since the rate of gastric emptying is dependent on resistance of the pyloric sphincter, further studies are needed to define stimuli to this physiologic sphincter mechanism.

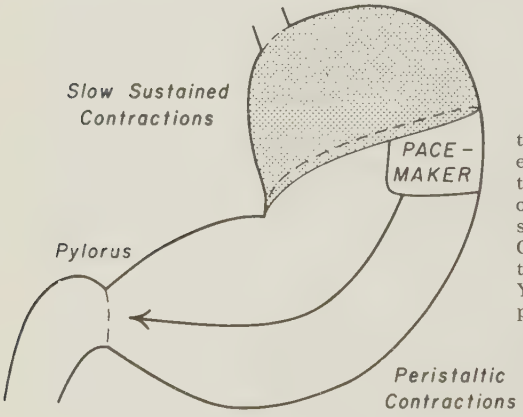

Figure 1. The proximal and distal portions of the stomach; control of emptying of liquids is regulated by the proximal stomach while emptying of solids is regulated by the distal stomach. (Reproduced from Kelly, K.: Gastric motility after gastric operations. Surgery Annual, 1974. New York, Appleton-Century-Crofts, 1974, pp. 103–123. Used with permission.)

Hormonal Factors

Hormones that arise in or act on the alimentary tract may alter gastric emptying. Although both in vitro and in vivo studies have been done, it is not clear whether these actions are physiologic or pharmacologic. Nearly all hormones studied have delayed gastric emptying. Gastrin, which increases the frequency of the pacemaker and causes action potentials to appear in the distal stomach, inhibits contractions and electrical activity in the proximal stomach. Its action is to delay gastric emptying.[11, 12, 18] Secretin, gastric inhibitory polypeptide (GIP), and cholecystokinin* inhibit peristalsis and delay gastric emptying.[8, 11] Motilin stimulates gastric motor activity, but whether the circulating concentrations are sufficient to effect gastric emptying remains to be determined.

Gastric Volume Receptors

Receptors in the gastric muscle that are sensitive to tension and distention were first described by Iggo[41] and Paintal in 1955 and 1954.[48] At least in sheep, as the stomach distends, these receptors emit impulses that are followed by gastric contractions. A greater number of impulses are released when the stomach is distended, but even when the stomach is empty one to ten impulses are discharged per second. These impulses are transmitted neurally and increase the rate of gastric emptying. Another vagal receptor in the gastric wall is both nonadrenergic and inhibitory (purinergic system).[11] The mediator in this system may be ATP and cyclic AMP, and it is postulated that the purinergic fibers facilitate gastric distention and receptive relaxation in the fundus.

Osmolarity

The earlier work of Carnot and Chassevant has been mentioned.[4] Studies by Hunt and his colleagues extended these early concepts.[33, 35] Many solutes were tested to determine the effect of osmolarity on gastric emptying.[49] These experiments suggested that sensitive duodenal osmoreceptors did delay gastric emptying. The solutes tested were glucose, sorbitol, sulfate, and salts of potassium, calcium, and sodium.[40] The effects of each of these substances were similar per milliosmol. Each slowed gastric emptying. When starch, glucose, and water were tested, both starch and glucose left the stomach more slowly than water.[36] It is postulated that the osmoreceptors are located in the duodenum deep to the brush border.

Acid Concentration

Acid solutions slow gastric emptying. The greater the concentration of acid, the greater the delay in gastric emptying. Hunt and Knox studied hydrochloric, acetic, lactic, phosphoric, tartaric, and citric acids.[10, 11, 13, 34, 37] The strength of the acid did not correlate with its effect on the rate of emptying. Acetic acid, a weak acid, was second to hydrochloric acid in delaying emptying. These investigators postulated that

*The action of cholecystokinin may be physiologic, as recently shown by Debas et al.[17a]

the anions determined the effectiveness of the acid in slowing emptying.

More recently, Cooke has shown that the first 5 cm of duodenum is sensitive to duodenal acidification.[10] His work suggested a neural feedback mechanism, since 0.2 to 0.4 mEq of acid could cause a rapid delay in gastric emptying. Schapiro and Woodward showed that this inhibitory response could be abolished by celiac ganglionectomy.[50] Further studies by Cooke and Clark suggested that the neural mechanism that delayed emptying was adrenergic, but that the receptor was neither alpha nor beta.[13]

The Effects of Fats

Fatty acids, particularly unsaturated fatty acids, delay gastric emptying. From acetic (C_2) to octanoic (C_8) acids there was little difference in the effect on gastric emptying.[14, 39, 52] In 10-to-14 carbon fatty acids there was a significant increase in ability to delay gastric emptying. Sixteen-to-18 carbon fatty acids (palmitic and stearic) were less effective in altering emptying. Whether the mechanism of action is neural, hormonal, or both is still undefined.[13]

Amino Acids

The effect of amino acids on gastric emptying was first studied by Thomas et al. in 1934.[51] More recently Cooke and Moulang[15] have done extensive studies on the effects of amino acids on gastric emptying. Of 22 amino acids studied, only L-tryptophan delayed emptying in concentrations that seemed physiologic under the conditions of protein digestion. Even amino acids that were potent liberators of cholecystokinin had little effect. An osmoreceptor in the duodenum was postulated to be the mechanism of action that delayed emptying for amino acids.

Thus, many factors including neurogenic, osmotic, hormonal, and concentrations of acids fats and amino acids are involved in the regulation of gastric emptying.

MEASUREMENT OF GASTRIC EMPTYING

Because of these many factors, it has been difficult to control and quantitate gastric emptying particularly when solid foods are used.

In principle, quantification of emptying may be done by (1) *intubation:* placing a known quantity in the stomach and periodically sampling it through a tube; (2) *radiologic tests:* measuring the amount of a radiopaque unabsorbed marker in the intestine; or (3) *isotopic studies:* measuring the amount of radioactivity emitted in a volume of gastric contents. There are practical limitations to each of these methods.

Intubation Tests

Sampling nasogastric contents and a dye marker from a nasogastric tube at intervals has been a common way of evaluating gastric emptying.[23] By calculating the amount and concentration of marker in each sample, the rate of emptying may be calculated, assuming the meal does

not separate from its markers (triglycerides may).[35] This method is reliable and reproducible but is limited because only liquids may be studied. Thus, the cephalic phase of secretion is bypassed.[47] Repeated intubation is necessary, an inconvenience for many patients. Many modifications have been made in this procedure including double sampling (George[22]), duodenal intubation and perfusion,[45] intubation plus isotopic studies, and modification of a solid meal maintaining it at a pH of 5.5.[63]

For widespread application, all of these modifications are limited because of the deficiencies inherent in the test, patient acceptance, or complex techniques.

Roentgenographic Studies

There are obvious advantages to using a barium meal in evaluating gastric emptying. It is relatively simple to do, well tolerated by the patient, available, and reproducible. The disadvantages outweigh the advantages. It is difficult to quantitate when the stomach is 25 per cent, 50 per cent, or 75 per cent full, since observer variation cannot be controlled. Liquids are easier to assess than solids. Attempts to mix barium with solid food brings criticism because barium may precipitate out of the meal. Finally, only total emptying time, that is, the time when all the barium has left the stomach, may be quantitated.

Isotopic Studies

Although radionuclide isotopic studies were used to measure gastric emptying 10 years ago,[22] it was not until 1970 with the application of the gamma camera that the method became more popular.[24, 28] Since then several authors have reported on their experience with radionuclide investigation of gastric emptying.[5-7, 9, 10, 27, 29, 30, 43, 53]

A variety of isotopes have been studied including chromium,[23] cesium,[16] iodine,[2] indium,[28-30] and technetium.[3, 6, 43, 53] The last two are used more frequently. DTPA (diethylenetriamine penta-acetic acid) is attached to both ^{99m}Tc and ^{113}In. The requirements for radionuclides used in studying gastric emptying are that the isotope should (1) not be absorbed through or absorbed to the gastric mucosa; (2) mix thoroughly with the ingested food; (3) not hasten or delay gastric emptying; (4) not be absorbed from the remainder of the gastrointestinal tract. Other factors besides cost and availability include the radiation dosage to the patient.

Emptying time will vary depending on what food the radioactive material is absorbed to or mixed with. Investigators have stressed the importance of establishing normal controls for a given meal.[43] Most have utilized the all-American meal of 20 grams of corn flakes, plus 150 ml of whole milk, and 15 grams of sugar.[6, 29] Exactly what portion of the meal the isotope is mixing with is unclear. Is the liquid phase or solid phase, or both phases, being measured? This has not been clarified.

Studies have shown that indium and chromium reflect different emptying rates with the former absorbing onto the solid portion of the meal and the latter into the liquid portion.

For the meal, gastric emptying time (GET) is expressed as one-half GET. This refers to the time that one-half the meal leaves the stomach.

Normal values with this meal are 37 ± 5 minutes.[6] Other investigators employing both technetium and indium with a more complex meal that includes ham and cheese, tea, bread and butter, a soft-boiled egg, and two cups of tea have found longer one-half emptying times that ranged from 23 to 77 minutes.[26, 53] This is because solids leave the stomach more slowly than liquids. Liquid meals (tap water and saline) tagged with ^{99m}Tc have shorter emptying times, being 15 minutes and 12 minutes respectively.[3, 7]

Several studies have shown that the isotope is not absorbed onto the gastric mucosa nor absorbed in the intestinal tract; the radiation dosage is very small, making the procedure relatively safe for patients. The radiation exposure is less than that during a barium enema study.[5, 29, 53]

Interpretation of data has also been variable depending on the patients studied and the isotope and meal used.

Our experience has been with the corn flake meal and ^{99m}Tc as the isotope. Our interest was stimulated by the report by Crowley et al. who assessed emptying in 30 patients from 1 month to 1 year after vagotomy and pyloroplasty.[16] Initially, the pattern of emptying was delayed in many patients but a wide scatter was present. At 1 year, the pattern was normal in seven patients. This sample is small and conflicts with other data that have shown that the early emptying rate was faster after vagotomy and drainage.[17] In another recent study using isotopes the rate of emptying was delayed after vagotomy and antrectomy but not after highly selective vagotomy.[42] Again, a recurring problem that makes it difficult to compare one study with another is the difference in meal, isotope, posture, and time from surgery.

We have evaluated 24 patients, both before and after vagotomy (truncal, selective, and highly selective) and some with postgastrectomy syndromes to assess emptying rates, particularly when surgery was planned. It was hoped that by using each patient as his own control, patterns of emptying reflecting different operations might emerge. To date, no pattern has emerged after any operation, but the sample and follow-up are small. As yet, there has been no early correlation between the rate of emptying by isotopic measurement and the clinical pattern. For illustrations and brief case summaries, Figures 1 to 6 are shown to dem-

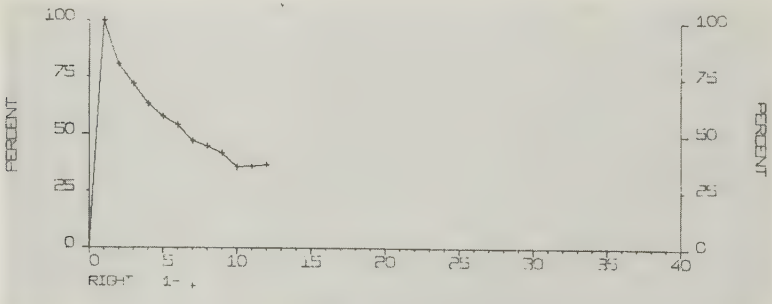

Figure 2. A normal pattern of gastric emptying. This study was done in a 50-year-old man prior to highly selective vagotomy. 50 per cent of the corn flake-technetium test meal has left the stomach in 35 minutes.

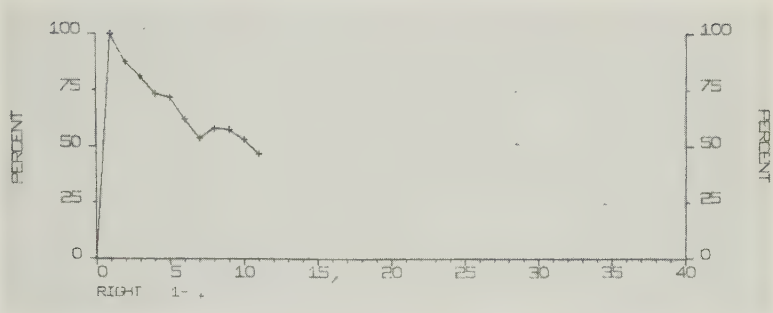

Figure 3. The same patient's gastric emptying pattern 72 hours after highly selective vagotomy without drainage. The early pattern of emptying is maintained and the curve is very similar to the preoperative study.

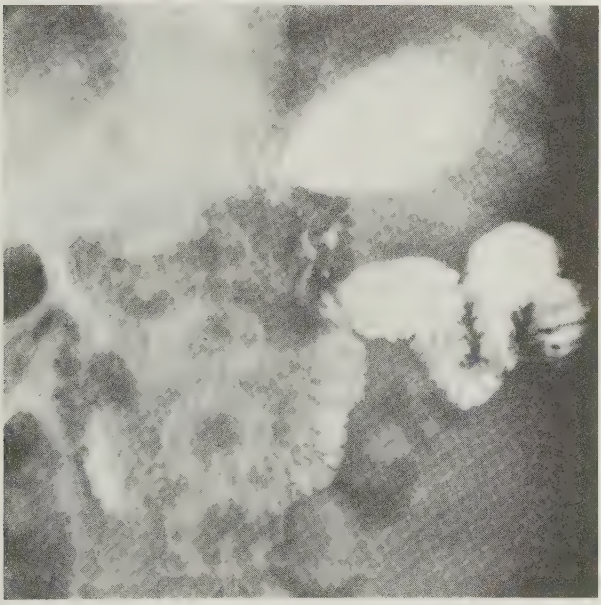

Figure 4. A 4 ounce barium swallow roentgenogram 48 hours after highly selective vagotomy in the above patient. It is difficult to quantitate how much barium remains in the stomach at this point in the study.

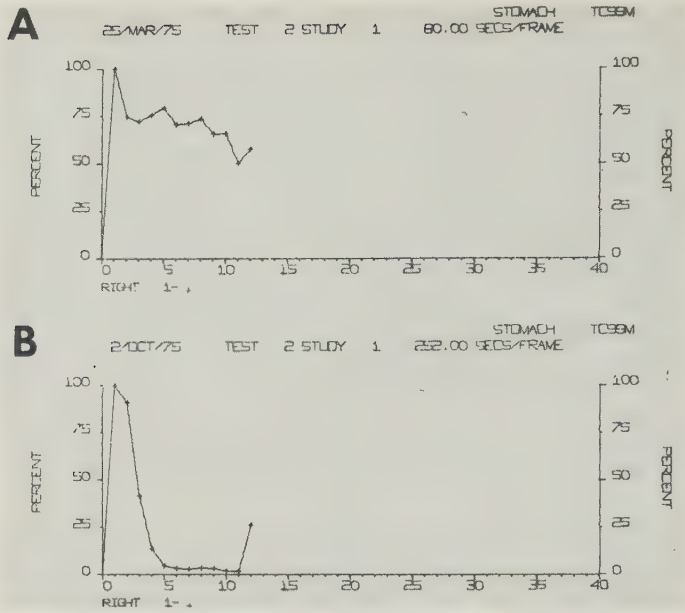

Figure 5. A 60-year-old man who underwent truncal vagotomy and pyloroplasty. The upper curve is a preoperative study. The lower curve shows rapid early emptying (this study was taken 3 months after surgery). He had no symptoms of dumping.

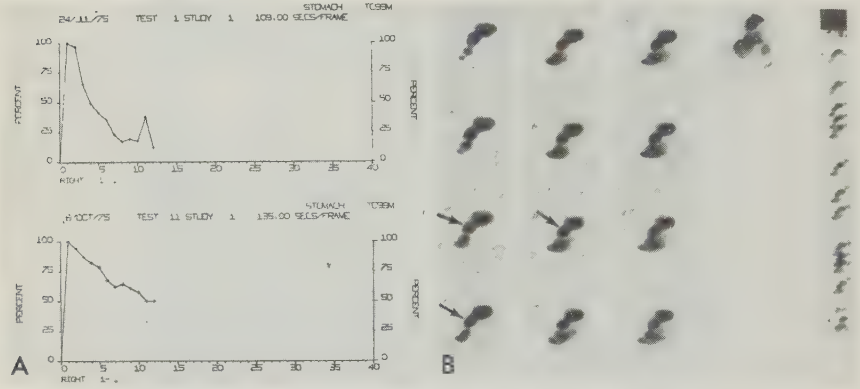

Figure 6. A 24-year-old man with symptoms of dumping, diarrhea and alkaline reflux gastritis following multiple gastric operations for duodenal ulcer. These included truncal vagotomy and pyloroplasty; hemigastrectomy; and interposed jejunal limb with conversion of a Billroth II to a Billroth I anastomosis. *A*, The upper curve shows rapid emptying before surgery. An antiperistaltic jejunal segment 10 cm long and conversion to a Roux en Y anastomosis and Billroth II anastomosis were done. The lower curve, taken 2 weeks postoperatively, shows a delay in emptying and a more normal curve. *B*, The concentration of the test meal in the antiperistaltic limb is seen (*arrow*). Despite this normal appearing curve the patient remained disabled due to persistent abdominal pain thought to be functional in origin.

onstrate the method and results. Further studies at varying times and a greater sample will be required; we are cautious about the clinical application of isotopic measurement of gastric emptying based on this limited and preliminary experience.

Newer Techniques

Malagelada et al.[45] have recently published data on a method that quantitates gastric secretion and emptying rates of a solid and liquid meal using constant duodenal perfusion with two nonabsorbable polyethylene glycol markers incorporated into the meal. Acid, pepsin, total gastric secretory rates, and the rate at which the meal and gastric sections empty have been quantitated. The methods for calculations and statistical analysis are beyond our comprehension, but these investigators showed that the stomach produced 800 cc of gastric juice in response to a 400 cc meal. Peak acid output occurred within 1 hour after eating and then decreased. Ten patients were studied and the method seems valid. It too was complex and the data are preliminary.

CONCLUSIONS

A variety of methods are available to assess gastric emptying. All have limitations. Intubation tests with newer modifications may allow quantification of gastric secretion and emptying. Of greater ease to the patient is radionuclide tests to assess emptying since intubation is not required. This test is not yet standardized. It varies with posture, meal, isotopes and time interval from surgery. Examples have been shown to demonstrate the technique and methods. Further information is needed and at present the clinical application of the test is limited and is used to understand physiologic changes in gastrointestinal disease.[49]

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Elective Surgery

"When knowledge is translated into proper action we speak of it as wisdom."
William Mayo, Surg. Gynec. Obstet., *30*:98–99, 1920.

"Similar results follow dissimilar operations."
George Hallenbeck

"Every operation for ulcer appears to be a success until it is found out."
Sir Ogilvie, as quoted.

"The foundation of modern gastric surgery was the exploratory incision."
William Mayo, Surg. Gynec. Obstet., *36*:447–453, 1923.

A Review and Evaluation of Operative Procedures Used for Chronic Duodenal Ulcer

*Stanley O. Hoerr, M.D.**

The modern gastric surgeon has available a variety of procedures which may be performed for chronic duodenal ulcer. Most surgeons agree that a vagotomy of some type should normally be performed to deal with the cephalic phase of gastric secretion. This is then normally accompanied by an additional procedure: a drainage operation to allow the atonic stomach to empty properly, or a limited distal gastric resection both to cope with atony and to eliminate the antral phase of gastric secretion. Some of the older generation of surgeons still rely on a subtotal gastrectomy (60 per cent more or less) without vagotomy as their standard operation. There continue to be circumstances where for one reason or another a satisfactory vagotomy cannot be performed, and it is well for us to remember that a subtotal gastrectomy without vagotomy will permanently relieve ulcer symptoms in 90 to 95 per cent of patients.[5]

Since the available operations have proven to be effective, in varying degree, with curing duodenal ulcer disease, all who do gastric surgery should be familiar with the numerous surgical options, be able to perform the various procedures competently, and to use the one which seems best for the specific patient undergoing an operation. In selecting the appropriate procedure, we must be aware of the pertinent features characterizing the various options.

Surgical procedures may be analyzed as to relative risk to life, effectiveness in curing the ulcer, freedom from significant side effects, and suitability from a technical standpoint for the specific anatomic situation. Enough information is available to permit the surgeon to make an intelligent choice.

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ANALYSES OF REPORTS

There are abundant reports in the literature of large series of patients who have undergone various operations for duodenal ulcer.[5, 8] The net effect upon the student of this disease and its surgical treatment may be one of confusion and perplexity, since the patient composition or fundamental design of one study may be quite different from that of another, precluding meaningful comparisons between them. Factors affecting a report include its method of selecting patients, retrospective or prospective approach, randomized selection, duration and completion of follow-up, as well as the manner in which the follow-up is conducted. My experience has taught me that the selection of patients may influence the results more than the selection of the operation. This fact is not emphasized in many reports and may not be ascertainable. And yet, to use an extreme example, if a given series contains a sizeable proportion of patients with minimal disease, the effect is first to reduce risk of surgery and hence the operative mortality, and second to improve results, since one would expect patients to do better generally than patients with severe forms of the disease. This lack of absolute standards makes it difficult to determine from published reports which operation, if any, is best.

Which Is the Safest Operation?

Although surgeons disagree about the incidence of side effects and recurrent ulcers following gastric operations, there should be few arguments about mortality rates. A death is absolute. Even so, as noted previously, patient selection has its effect. Most reports distinguish between mortality rates of operations performed electively and those done as an emergency. Today with improved anesthesia, better preoperative and postoperative pulmonary care, and careful selection of patients, all ulcer operations should be comparatively safe with a mortality rate less than 1 or 2 per cent. Several large controlled randomized series have shown no differences in operative mortality between gastric resection or vagotomy and drainage.[5, 13] This does not mean that all operations are equally safe for a given patient. Exclusion of some patients because operative findings make a gastric resection hazardous is permissible even in randomized studies, as it should be. Thus the judgment and experience of the operating surgeon are important factors even if hidden in these randomized studies as well. Second, most prospective studies are conducted by gastric surgeons who have had extensive experience with all ulcer operations. The results of these studies will not represent the mortality rates likely to be achieved by less experienced surgeons. My observations are that lesser operations (vagotomy and drainage) inevitably result in fewer deaths than procedures involving a gastric resection. In the largest series from this country, the mortality rate after 3500 truncal vagotomy and antrectomy operations was 1.6 per cent while after 1000 truncal vagotomy and draining procedures it was 0.5 per cent.[7]

Which Operation Has the Highest Cure Rate For Ulcers?

The longer the follow-up, the greater the incidence of recurrent ulcers following operations for duodenal ulcer. In my experience I have seen a marginal ulcer appear after 26 symptom-free years following a gastric resection. Such cases are very unusual, however, and sufficient time has elapsed following the introduction for all currently employed procedures, except proximal gastric vagotomy, to permit legitimate evaluation of their effectiveness in curing the ulcer. There is a general conviction among surgeons that vatogomy combined with resection has the lowest incidence of recurrent ulceration, and this is supported by many reports with higher recurrence rates following vagotomy and drainage.[5, 7, 13] Even here the issue is clouded by the possibility that many recurrences following vagotomy and drainage may be due to incomplete or "inadequate" vagotomies, although recurrences can and do take place after a complete vagotomy. The technical proficiency of surgeons varies, and the infrequent use of postoperative tests to assess the completeness of the vagotomy means that many surgeons have no accurate idea as to how "adequate" a vagotomy they have performed.[11]

Like tests for completeness of vagotomy, accurate quantitative studies of preoperative acid secretion are infrequently employed, and have not proved useful in predicting the likelihood of recurrent ulceration in a given patient. A reliable test of this sort would be most helpful in directing surgeons to a maximum first operation (i.e., vagotomy and resection) in those patients demonstrably prone to recurrence by reason of very active gastric acid production.

Finally, the reported recurrence rates with each operation are very variable. The recurrent ulcer rate after various operations has been summarized by Johnson.[9] After gastric resection alone it has varied between 0.9 and 15 per cent; after vagotomy and drainage 2.2 to 27.3 per cent and after vagotomy and resection 0 to 3.3 per cent. But despite such variability, most careful studies have consistently shown the lowest recurrent rates after vagotomy and resection.[9] Proximal gastric vagotomy will be discussed separately.

Do the Postoperative Symptoms Differ With Each Operation?

As Hallenbeck summarized, "Similar results follow dissimilar operations."[6] The Leeds-York study which compared subtotal gastric resection, vagotomy and antrectomy, and vagotomy and drainage showed the incidence of epigastric fullness, bile vomiting, and nausea to be similar after each operation. As anticipated, greater weight loss followed gastric resection (with or without vagotomy) than vagotomy and drainage. Diarrhea occurred more commonly after vagotomy than after resection alone. These findings have been substantiated in other reports.[6] My experience supports this and the existence of such sequelae detract from the subjective result in some 10 per cent of patients.[8] Certainly the anticipated decrease in many of these sequelae following vagotomy and drainage has not materialized.

Which Vagotomy?

Today interest centers around which type of vagotomy should be done. Three vagotomies are available; truncal, selective, and highly selective. Truncal or total abdominal vagotomy is the one most widely used today. It is usually the simplest to perform, especially in the obese patient, and is relatively free from disabling side effects, although significant diarrhea may occur in an occasional patient (a probable incidence of not more than 1 or 2 per cent in my experience). Selective vagotomy or total gastric vagotomy, which preserves nerve branches to the liver and celiac plexus, has been carefully studied in several centers but most surgeons have not taken the trouble to master the technique. They have felt that it has yet to be proven superior to truncal vagotomy. From a theoretical standpoint, selective vagotomy is superior to truncal vagotomy in that it spares nerves not stimulating the parietal cells of the stomach. This may have a role in preventing ill-defined malfunctions involving the liver, pancreas, and bowel. One would anticipate in selective vagotomy an even lower incidence of disabling diarrhea, and most studies comparing selective and truncal vagotomy have shown this to be true.[12]

Some investigators familiar with both truncal and selective techniques report more consistent results in reducing gastric hypersecretion and recurrent ulceration following selective vagotomy, and have attributed this to a more complete anatomic gastric vagotomy than is accomplished with truncal vagotomy. These reports have recently been summarized by Cooperman.[3] After an experience with more than 700 truncal vagotomies, I find this difficult to believe. A more intriguing and satisfying explanation to me has based the success of this operation on physiologic and not anatomic reasons. Kelly et al.[14] suggested in 1966 that selective vagotomy by leaving the celiac nerves intact might allow release of a humoral substance that could inhibit gastric secretion. This could be lost with truncal vagotomy. Whether this mediator is secretin, enteroglucagon, vasoactive intestinal polypeptide, gastric inhibitory peptide, or other candidate hormones is not yet known.

Highly selective vagotomy, ultra selective vagotomy, parietal cell vagotomy, or *proximal gastric vagotomy* all describe the same operation: denervation of the proximal half of the stomach with preservation of the nerves of Latarjet supplying antrum and pylorus. From a theoretical standpoint this vagotomy is the most attractive of all since it destroys only the nerves directly stimulating the acid-producing parietal cells. There have been enthusiastic reports on large series of patients both from England and Denmark, and the operation is being tested clinically in several centers in the United States.[1, 2, 4] It seems to be successful in many patients without the addition of a drainage procedure, an obvious advantage over both truncal and selective vagotomy. It is conceptually simple, and is certainly as safe as any operation for duodenal ulcer. Of the 5539 cases summarized by Johnston,[10] the operative mortality has been 0.3 per cent. Another attractive feature is that it is most unlikely to produce irreversible damaging side effects. Certain questions can only be settled by careful follow-up studies and the elapse

of time. Will proximal gastric vagotomy prove to be as effective in severe ulcer disease as the more extensive operations? If not, what are the indications for its use? Certainly the theoretical advantages have been substantiated in clinical trials. Diarrhea, dumping, epigastric fullness, and bile vomiting are reported to occur less often than following other gastric operations. The technique of performing proximal gastric vagotomy is of great importance, and as with any new and different procedure, those surgeons wishing to try it should first learn how to do it, no matter how proficient they may be in truncal vagotomy and gastric surgery. It may also be wise for surgeons not working in centers to permit more time to elapse for its evaluation by those surgeons studying it.

Antrectomy or Drainage?

Currently in this country, the most popular operation for duodenal ulcer is antrectomy or limited distal gastrectomy (25 to 40 per cent) of the stomach (depending on the surgeon who is doing the estimating), combined with truncal vagotomy. The reconstruction may be either of the Billroth I or Billroth II variety. The end results of this operation have been thoroughly studied by many different surgeons with the unanimous observation that it is one of our most effective procedures for eradicating the ulcer diathesis.[7, 13, 15] The incidence of recurrent ulceration is rarely reported as greater than 1 or 2 per cent. Yet there are disadvantages to be considered. In my experience, as previously noted, any type of gastric resection for chronic duodenal ulcer, even when performed electively, will result in a higher mortality rate than do the various drainage procedures. My mortality rate for elective vagotomy-hemigastrectomy (my experience is confined to the Billroth II reconstruction) is just over 3 per cent, as opposed to 0.7 per cent for vagotomy-drainage.[8] Experienced gastric surgeons agree that a gastrectomy should be avoided if the pyloric area is involved in an inflammatory mass, and under these circumstances will by choice use a drainage procedure such as a gastroenterostomy to avoid a technically difficult and dangerous operation. Another factor to be considered is that increased incidence of weight loss, reflux gastritis, and probably dumping occurs after this operation; it may be wise to avoid a gastric resection in patients with a marked functional overlay.

Which Drainage Procedure?

Conventional two-layer (with inversion of the inner layer) Heineke-Mikulicz pyloroplasty did not work well with truncal vagotomy, until Weinberg[16] introduced the single-layer anastomosis which resulted in a larger lumen and permitted better gastric emptying. I still use this pyloroplasty if there is little or no scarring in the pyloric area, because it takes advantage of the antral contractures. The Finney pyloroplasty, in my experience, has a somewhat better record in long-term results than the Heineke-Mikulicz, and a wider applicability. The Jaboulay procedure, a side-to-side gastroduodenostomy, is a modification of the Finney pyloroplasty (merely avoiding cutting across the pylorus). In recent years I have used it more than either the Finney or the Heineke-Mikulicz. It is especially useful if there is scarring or inflammation

localized to the pyloric area, when the Finney or Heineke-Mikulicz pyloroplasties should not be attempted. An incidence of recurrent ulceration of up to 10 per cent is to be expected after any one of these drainage procedures with a truncal vagotomy, and another operation is required to correct it in at least half the patients with recurrent ulcer. One should use the drainage procedure which seems to be appropriate; if all are suitable, one should use the one with which he is most familiar and satisfied.

A gastrojejunostomy may be the preferred drainage procedure if scarring or inflammation renders dissection of the pyloric area difficult and dangerous. A variety of gastrojejunostomies is available: antecolic, retrocolic, dependent, isoperistaltic, antiperistaltic cross-cut. I prefer the antecolic dependent cross-cut gastrojejunostomy to be placed near the pylorus at the greater curvature of the stomach in the majority of instances where this type of drainage procedure is indicated. The technical ease of accurate placement of the gastrojejunostomy without becoming involved with the mesocolon has appealed to me. The results in my hands have been equivalent to retrocolic gastrojejunostomies, despite a presumed theoretical advantage of a shorter jejunal loop in the latter. In a lengthy follow-up experience, proved or probable recurrent ulceration has taken place in more than 13 per cent of the patients, with a second operation required in about 8 per cent.[8] Although gastrojejunostomies have fallen out of favor, I believe surgeons will do well to bear them in mind, and to consider using one in the occasional situation where it is best and safest. In the study of Goligher et al.[5] it proved superior to pyloroplasty when accompanied by truncal vagotomy.

PERSONAL RESULTS AND OBSERVATIONS

Over the past 25 years I have operated upon more than 650 patients for duodenal ulcer disease with a long-term follow-up of about 95 per cent.[8] A pattern has emerged in that in terms of patient satisfaction (irrespective of recurrent ulceration which can almost always be corrected by another operation—usually a gastric resection if not done previously) there appears to be a permanent group of about 10 per cent of patients who are not happy with the results, no matter which operation was done. This applies equally to vagotomy-antrectomy and to vagotomy-drainage. It is also apparent in my results of surgery for gastric ulcer, where recurrent ulceration is rare: about 10 per cent unhappy patients. I suspect it will be found to apply to "proximal gastric vagotomy" as well, since this is a group of patients with a combination of temperamental factors and functional gastrointestinal symptoms unlikely to yield to any type of treatment, including psychotherapy and surgery. My personal bias through the years has been to perform any of the operations referred to in this paper (except proximal gastric vagotomy, with which I have had no experience) as the circumstances seemed to warrant. I went through a period (1950-1952) during which I was performing mostly truncal vagotomy and posterior gastrojejunostomy, but occa-

sional gastric resections as well. When the rate of recurrent ulcerations seemed to be unacceptably high, I turned for a period of years (1953-1957) to truncal vagotomy and hemigastrectomy. When some patients in this group died that I thought might have survived a simpler operation (no gastric resection), I embarked upon truncal vagotomy and pyloroplasty (1958–1966) as the procedure of choice, again using other operations as it seemed appropriate. In 1967 truncal vagotomy with the Jaboulay procedure became my favorite, but with many instances of the other operations interspersed. If I were a younger surgeon, I would learn the technique of proximal gastric vagotomy and use it where it seemed to be the best choice.

Factors other than the procedure performed affect long-term results. There has been a widespread belief that, for whatever reason, women do not do as well as men following gastric surgery. This belief is substantiated in my own practice, where poor results in women are twice as frequent as they are in men, and not necessarily due to recurrent ulceration. To me this has meant an avoidance in women of a gastric resection, with its higher incidence of postoperative gastric woes. It has also suggested to me that women whose operations are performed for intractable pain, and who have no evidence of obstruction, may well be the best candidates for proximal gastric vagotomy without drainage.

An unexpected finding in my follow-up studies was that if the principal indication for vagotomy and gastrojejunostomy had been obstruction, a second operation was needed in less than 2 per cent of the patients, whereas if vagotomy and gastrojejunostomy were done in a patient who had had serious bleeding in the past, second operations for recurrent ulcer were done in 15 per cent! This fact has made me lean toward vagotomy with antrectomy for patients who had a history of hemorrhage, whereas it would seem to be unnecessary to perform the more extensive operation for simple obstruction.

CONCLUSIONS

It should be clear from the foregoing that no one operation has emerged as the one to be used for all patients requiring surgery for chronic duodenal ulcer, although currently the favorite appears to be truncal vagotomy with antrectomy. The last word is not yet written on the place of selective and proximal gastric vagotomy: they may well assume an increasingly important position in the armamentarium of the surgeon.

Let us stay open-minded and flexible, and let us consider all factors that might apply to the patient we are operating on in deciding what we are going to do: risk of death, sex, technical difficulty, and reason for operation including obstruction (bias toward vagotomy-drainage) and hemorrhage (bias toward vagotomy-antrectomy). Let us keep accurate records and report our long-term results accurately and completely so that others may benefit not only by learning of our successes but also of our failures.

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Facts and Heresies About Vagotomy

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When a surgeon opts to perform a vagotomy, on what basis does he make his decision? Vagotomy is always optional: alternative procedures are available in each surgical situation. As newer and more refined vagotomy techniques become available, by what criteria should they be judged? To provide an interim background picture for the surgeon we make in this article a number of statements which we have labelled "facts" or "heresies" according to our assessment of the available evidence.

FACTS

1. Vagotomy Is Safe

We surveyed the available literature[19] and in published reports and we found an operative mortality of 0.8 per cent in 6490 patients who had elective truncal vagotomy and drainage, and 1.6 per cent in 1725 patients who had truncal vagotomy and antrectomy. The operative mortality for elective partial gastrectomy is at least 1 to 2 per cent. Published reports have confirmed this trend, although in clinical trials by experienced gastric surgeons zero mortality has been achieved for elective gastrectomy.[28]

2. Proximal Gastric Vagotomy Is Safest

Johnston[40] recently wrote to 43 surgeons who perform the new operation. Each replied, and as a group reported 17 deaths after 5539 elective operations (0.3 per cent). The causes of death were: necrosis of the lesser curve or fundus (5), myocardial infarction (4), pulmonary embolism (3), pneumonia/respiratory failure (2), one death each of intraperitoneal haemorrhage, erosive gastritis and mesenteric vascular occlusion. We have had no deaths in our series.

Johnston compared this overall mortality of 0.3 per cent with our

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mortality estimates from published reports[19] of 0.8 per cent with truncal vagotomy and drainage, and 1.6 per cent for truncal vagotomy and antrectomy.

One-half the 17 deaths were due to thrombosis or embolism, and Johnston suggested that these might have been prevented by low-dose heparin. Five of the deaths were due to necrosis of the lesser curve or fundus, presumably an ischemic complication of baring the lesser curve in this operation, and particularly frequent in patients in renal failure.

3. Proximal Gastric Vagotomy Has Least Sequelae

Postoperative. In a collected series of 5539 patients[19] there was delay in gastric emptying lasting 3 days or more in 0.7 per cent in the early postoperative period, and seven of these 36 patients (0.1 per cent) needed reoperation. Another 35 needed a drainage procedure in subsequent months, for a total reoperation rate for retention of 0.8 per cent.

Follow-Up (Table 1). In the two controlled trials of comparing proximal gastric vagotomy against selective vagotomy and drainage with either pyloroplasty[55] or gastrojejunostomy,[50] the incidence of all postvagotomy sequelae was less, and usually significantly less, in the proximal gastric vagotomy group. Severe dumping and diarrhea occurred rarely, if at all. The more frequent and more severe side effects noted after selective vagotomy may not have been due to denervation of the antrum in this procedure as compared with proximal gastric vagotomy, but may have been due to the associated drainage procedure. To date, the rational basis of the new vagotomy in leaving an innervated antral pump, and an intact pylorus, seems borne out by a low incidence of postoperative sequelae. In our unpublished series the incidence of Visick I grading is significantly higher after proximal gastric vagotomy than after truncal vagotomy and antrectomy.

Moreover, patients after proximal gastric vagotomy showed a mean increase of nearly 3 kg in weight the year after operation, whereas the control group, after truncal vagotomy and antrectomy, had a mean loss of nearly 2 kg. The difference in weight change between the two groups was statistically significant.

4. Proximal Gastric Vagotomy Is an Effective Acid-Reducing Operation

The reduction in acid output after proximal gastric vagotomy is about 80 to 90 per cent for basal, 50 to 60 per cent for pentagastrin, and 60 to 90 per cent for insulin-stimulated secretion (Table 2). These reductions are similar to those after selective vagotomy in controlled trials, and to selective or truncal vagotomy and antrectomy, or after partial gastrectomy with or without vagotomy.[6] The residual absolute values for basal, pentagastrin, and insulin-stimulated acid outputs are also similar, and serial measurements of acid secretion over the few years since proximal gastric vagotomy has been first performed have shown little variation with time.

Thus the new vagotomy is as effective in reducing gastric acid secretion as the older vagotomies, but no better. If reduction of acid allows duodenal ulcers to heal, and if the smaller the reduction the

Table 1. *Controlled Trials of Proximal Gastric Vagotomy (Highly Selective Vagotomy) and Selective and Truncal Vagotomy*

REFERENCE SOURCE	WASTELL ET AL.[75] 1974		KOFFMAN ET AL.[52] 1975		KRONBORG AND MADSEN[55] 1975		HOPTON ET AL.[35] 1976		KENNEDY ET AL.[50] 1975	
Operation	PGV	PGV+P	HSV	TV+P	HSV	SV+P	HSV	TV+P	PGV	SV+GJ
n	52	48	45	45	50	50	25	21	50	50
Follow-up Years	1–4				1–4		1–3		1–4	
Operative mortality	0	0	0	0	0	0	0	0	0	0
Recurrent ulcer										
definite	2	2	1		11 *	4			1	1
?			2	2					1	
Total	4%	4%	7%	4%	22%	8%			4%	2%
Diarrhea										
mild	13%	4%	8	22%	6% *				4%	10%
severe	0	0	0	0	2%	12%			0	2%
Epigastric fullness	17%	23%			8% †	28%				
Nausea									10% *	28%
Vomiting										
food	7%	7%			4%	14			10%	10%
bile									2% *	14%
Dumping										
mild	10%	23%			4% ‡	10%			8% ‡	29%
severe	0	9%			2% ‡	20%			0 ‡	8%
Heartburn									14%	16%
Flatulence									18%	32%
Visick I	63%	36%			68%	40%	60%	42%	60%	33%
II	28%	40%			10%	28%	20%	29%	36%	42%
III	0%	16%			21%	24%	12%	24%	2%	18%
IV	9%	8%			20%	8%	8%	5%	2%	6%
I + II	91%	76%			78%	68%	80%	71%	96%	76%

*P < 0.05. †P < 0.01. ‡P < 0.001.

Table 2. *Gastric Acid Secretion After*

Source	Date	Timing Months	n	Proximal gastric vagotomy		
				Basal mmol per hr per cent reduction	Maximal mmol per hr per cent reduction	Insulin mmol per hr per cent reduction
Liavag and Roland[56]	1971	2–3	41	1.2 72%	13.7 64%	
Liavag and Roland[57]	1973	12–24		71%	56%	
Moberg and Hedenstedt[61]	1972	1	63		75%	
Wastell et al.[74]	1972	1/3	16		14.5 58%	
Wastell et al.[75]	1974	1/2	47		15–22 44–58%	
Clark et al.[12]	1973	1/2	16	3.1 21%	11.6 70%	
Imperati et al.[36]	1972	1/3	81	1.8 81%	11.4 69%	
Grassi et al.[29]	1973	3–24	62		80–85%	
Johnston et al.[46, 47]	1973	1/4	27	0.4 92%	13.6 56%	0.5 86%
		2–3	48	0.6 88%	10.8 68%	1.3
		6–12	24	0.5 87%	15.2 55%	3.2
		12–24	46	1.1 80%	15.5 56%	3.6
Clarke et al.[15]	1972	3	20	0.8 74%	12.6 71%	1.2 96%
Kronborg and Madsen[55]	1975	1/3	50		19.7	
Stadaas[70]	1975	3	10	1.4 88%	15.6 62%	
Vatn et al.[73]	1975	2	7	1.4 67%	16.1 44%	10.1 61%
Lyndon et al.[59]	1975	36 60	17 20			3.1 3.5

Proximal Gastric Vagotomy

PROXIMAL GASTRIC VAGOTOMY			CONTROLLED TRIAL COMPARISON				
Insulin—Basal mmol per hr per cent reduction	Operation	n	Basal mmol per hr per cent reduction	Maximal mmol per hr per cent reduction	Insulin mmol per hr per cent reduction	Insulin – Basal mmol per hr per cent reduction	
	PGV+ Pyloro-plasty	20		16.9 56%			NS
		41		16–41 57%			
100%							
	Selective Vagotomy	20	15.7 80%	1.1 61%	2.2 92%	42%	NS
4.2	Selective Vagotomy	50		20.3 57%		4.2	NS

higher the recurrent ulcer rate, then proximal gastric vagotomy should have an incidence of recurrent ulcer similar to other vagotomies.

5. Long-Term Results of Proximal Gastric Vagotomy Are Uncertain

The recurrence rate after proximal gastric vagotomy has been reported from ten centers, but in all of these the length of follow-up is a few years only and the criteria for recurrent ulcer vary. The extent of denervation in centimeters from the pylorus has also varied in different centers, as has the reduction in acid secretion.

From the uncontrolled series one might infer that the incidence of recurrent ulceration is probably as low as, or lower than that of other vagotomies; a similar inference can be drawn from the few controlled trials (Tables 1 and 3). Recurrence after truncal vagotomy may appear late, so we need longer follow-up before coming to any long-term definitive assessment.

However, no operation to date for the treatment of duodenal ulcer has yielded a high ultimate incidence of recurrence following a low initial recurrence rate. Indeed, although with some operations "recurrence" has been seen as late as 30 years after surgery, after all operations most recurrences (by which term we include stomal ulcers if gastroenterostomy has been performed) were within the first 2 years after operation.

Against this background it seems unlikely that proximal gastric vagotomy will produce a higher recurrence rate than vagotomy and drainage, although recent trends suggest it may be about the same. These inferences may be incorrect, and no firm conclusions can be drawn concerning the long-term results of this operation until much larger 5-year follow-up series are available.

HERESIES

6. All Vagotomists Are Equal

There have been two studies of the results of insulin tests after operations by surgeons in the same center but of different experience. In Sheffield[49] there were "early positive" Hollander responses[66] in 13 of 54 patients whose vagotomies had been performed by surgeons in training, but in none of 73 patients vagotomised by experienced surgeons. One of Kay's surgical trainees' first 24 vagotomies showed the following pattern of early positive/negative responses:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
+	+	−	−	+	+	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−

However, in nearby Leeds[41] the mean percentage of "incomplete" truncal vagotomies (positive Hollander) by nine consultant surgeons (18 per cent) was higher than those of 15 senior registrars and registrars (12 per cent), even though the range was smaller in consultants (8 to 45 per cent) than in their assistants (0 to 52 per cent). Results after selective

Table 3. *Recurrence of Ulcer After Proximal Gastric Vagotomy for Duodenal Ulcer*

SOURCE	DATE	n	FOLLOW-UP YEARS	RECURRENT ULCER DEFINITE n	DEFINITE Per cent	?	TOTAL	PER CENT
Grassi and Orecchia[29]	1973	78	1/4–2	1	1%		1	1%
Liavag and Roland[57]	1973	272	0–3				0	0
Moberg and Hedenstedt[62]	1973	51	3				3	6%
Amdrup et al.[5]	1974	108	2–4	2	2%	3	5	5%
Wastell et al.[75]	1974	100	1–4	4	4%		4	4%
Kennedy et al.[50]	1975	50	1–4	1	2%		1	2%
Kirk[51]	1975	61	1/2–5	2	3%		2	3%
Koffman et al.[52]	1975	45	1	1	2%	2	3	6%
Kronborg and Madsen[55]	1975	50	0–4	11	22%		11	22%
Lyndon et al.[59]	1975	100	3 1/2–6 1/2	1	1%	4	5	5%
Madsen and Kronborg[60]	1975	200	1					10%
Heffernan[33]	1976	260	0–5	4	1.5%			1.5%
Desmond[20]	1976	141		0	0		0	0

vagotomy were similar, but there was a marked decrease in the incidence of positive Hollander responses after selective vagotomy during the years 1966 to 1970.

In Lund[58] the operation of proximal gastric vagotomy has been performed either by two gastric surgical specialists or by 18 "general" surgeons (Table 4). Two months after the operation, the 60 patients operated by general surgeons showed significantly higher basal, peak pentagastrin, and peak insulin-stimulated acid output than the 39 patients operated by gastric surgeons. One year after vagotomy not only were the differences still present, but the patients operated on by "general" surgeons had more than twice as much acid in response to insulin as the patients operated by gastric surgeons, and also showed five times the incidence of recurrent ulceration.

Until recently vagotomists used the qualitative criterion that an insulin test yielded either a positive or a negative result, and that vagal innervation was either present or absent. It is now more generally recognized that a surgeon does not cut all or none of the vagal fibers to the stomach, and that the higher the peak acid output the more parasympathetic fibers remain. This quantitative approach to vagally mediated gastric secretion is only presumptive in man, but now has experimental support.[63-65]

Acid tests are therefore of value to the surgical team in assessing the completeness of their vagotomies; this may help to improve technique and reduce the incidence of recurrent ulceration.

7. Vagotomy Cures Gastric Ulcer

Classification

Gastric ulcer is probably multifactorial in etiology as well as a heterogeneous disease. A distinction should probably be made[38, 39] between:

I. *Ulcers of the body of the stomach* associated with gastritis and hyposecretion. The rationale of partial gastrectomy for such gastric ulcers is not to correct hypersecretion, as in duodenal ulcer disease, but to remove the ulcer and that part of the stomach most susceptible to ulceration. Both gastrectomy and vagotomy aim to reduce the already low gastric acid secretion still further, so that peptic digestion of the gastritic residual gastric mucosa is prevented. An incidental aim is also to remove the ulcer to confirm that it is benign.

II. *Prepyloric ulcers of the antrum*, usually associated with gastric hypersecretion, and possibly best treated by surgeons (by vagotomy and/or resection) as if they were duodenal ulcers.

III. *Gastric ulcers associated with duodenal ulcers*, which may be associated with duodenal ulcer-like hypersecretion, and therefore possibly treatable with an acid-lowering procedure.

Vagotomy and Acid Reduction. After truncal vagotomy in 25 patients basal acid output was reduced by 80 per cent, and maximum histamine acid by 73 per cent in 11 prepyloric/body ulcers, and 81 per cent in seven combined ulcers. One of the patients with gastric ulcers failed to heal and was shown to have an incomplete vagotomy. One of the seven patients with combined ulcers needed a further gastrectomy for recurrence and was shown to have a complete vagotomy.[27] Truncal

Table 4. *Basal, Pentagastrin and Insulin-Stimulated Gastric Acid Output (Mean ± SEM) in Patients with Duodenal Ulcer in Lund, 60 Operated by 18 General Surgeons, and 39 by Two Gastric Surgeons (Liedberg and Oscarson[58])*

	BEFORE OPERATION		AFTER PROXIMAL GASTRIC VAGOTOMY			
			2 MONTHS		12 MONTHS	
	General	Gastric	General	Gastric	General	Gastric
Basal Acid Output mmol per hr	7.5±0.7	5.7 ± 0.6	1.9 ± 0.4	1.0 ± 0.2	2.3 ± 0.4	1.7 ± 0.2
per cent reduction			58 *	82	49	70
Peak acid output after Pentagastrin – mmol per hr	33.9 ± 1.6	35.2 ± 1.6	20.7 ± 1.5	16.1 ± 1.0	21.9 ± 1.5	20.3 ± 1.1
per cent reduction			39 *	54	35	42
Peak acid output after Insulin – mmol per hr			6.4 ± 1.1 †	1.8 ± 0.3	9.4 ± 1.2 †	4.3 ± 0.6

*P < 0.05.
†P < 0.001.

vagotomy reduced maximum pentagastrin-stimulated acid output by 65 to 70 per cent and healed each ulcer in 16 patients with combined gastric and duodenal ulcers.[76] In 50 patients with gastric ulcers alone truncal vagotomy was added to pyloroplasty in those 22 with peak acid output after histamine more than 15 mmol per hr, with a 76 per cent reduction in peak acid output and no recurrence in a 1 to 9 year follow-up.[1]

Proximal gastric vagotomy reduced basal acid output by 76 per cent and peak pentagastrin output by 66 per cent in 14 patients with gastric ulcer alone and 57 per cent in four patients with combined ulcers[42] and similar reductions (basal 90 to 100 per cent; maximal 75 per cent) were seen in 32 patients with types I and III gastric ulcers.[32]

Pyloroplasty. Patients with gastric ulcer have been treated by pyloroplasty alone, but with high rates of recurrence, e.g., three of three patients,[77] four of 18,[53] two of four.[71] When pyloroplasty alone was done in patients with gastric ulcer alone with peak acid output after histamine less than 15 mmol per hr, four of 28 recurred in a 1 to 9 year complete follow-up.[1]

Vagotomy for gastric ulcer was introduced by Harper and Dragstedt.[30] In a comparison of published uncontrolled series Duthie[21] noted that the mortality of the 375 vagotomies (1.4 per cent) was lower than the 1252 Billroth I partial gastrectomies (1.8 per cent), but the recurrence rate was higher after vagotomy (5.2 per cent) than after gastrectomy (1.5 per cent). Duthie et al.[22] therefore carried out a randomized controlled trial without operative deaths in either group, but with significantly greater immediate postoperative morbidity and a significantly longer hospital stay in the 50 patients treated by 50 per cent Billroth I gastrectomy than the 50 treated by truncal[40] or selective[9] vagotomy and pyloroplasty.

A 5-year follow-up[23] revealed that five patients had recurrent ulcers after vagotomy (three required reoperation) and two had recurrences after gastrectomy (both treated medically). Four other vagotomized patients required later gastrectomy (three for gastric cancer, one for hemorrhage, and one for persistent diarrhea), a total of 7 reoperations after vagotomy, and none after gastrectomy. Overall good results (Visick I and II) were found in 78 per cent after gastrectomy and 68 per cent after vagotomy, with bad results (Visick IV) in 8 per cent after gastrectomy and 20 per cent after vagotomy. This difference did not quite reach a level of statistical significance but allowed the conclusion that "No evidence has been provided to support the abandoning of Billroth I partial gastrectomy in the treatment of gastric ulcer."

Conclusion. There are only scanty data on the acid-lowering effects of different types of operation for gastric ulcers, and indeed it is not certain that acid reduction is the principal objective of operations for this disease. At present, therefore, a rational policy is not possible, and we empirically prefer a Billroth I partial gastrectomy to a vagotomy and drainage operation, guided by comparisons between these two procedures in the published literature and in the controlled trial. Whether or not controlled trials eventually show an acceptable recurrence rate of gastric ulcer (or carcinoma) after a vagotomy, it seems probable that patients will have less sequelae such as steatorrhoea after

proximal gastric vagotomy.[24] Bleeding gastric ulcers may well be treated best by vagotomy and pyloroplasty.[16]

8. Vagotomy Is for Normosecretors

More than two-fifths of 75 British gastroenterological surgeons,[9] and more than four-fifths of a sample of gastric surgeons in the United States[8] did acid tests in patients with duodenal ulcer and then used vagotomy only in normosecretors, and performed additional antrectomy or a partial gastrectomy in the hypersecretors. We do not agree with this practice.[7]

There is a wide range of maximum acid output in patients with chronic duodenal ulcer. One aim of gastric surgeons is to reduce gastric acid secretion below an ulcer threshold. If acid-lowering operations tend to reduce gastric acid by a fixed amount or a fixed percentage, a patient with a high acid output needs an operation with a more acid-lowering effect than a patient with a lower acid output.[6]

Somervell and Orr[69] introduced the concept of *selective surgery* for duodenal ulcer by advocating gastrojejunostomy for patients without very marked hyperacidity, and partial gastrectomy for those with excess hyperacidity. There have been more than 13 such schemes in which various increasingly radical operations with greater acid-lowering effect have been used for patients with higher acid outputs. A review of their results[6] found few convincing follow-up studies. Carefully collected data came from Edinburgh[68] where about 25 per cent of patients who used to be subjected to Polya gastrectomy are now treated by other operations with, however, only slight reductions in mortality and recurrent jejunal ulceration.

An adequate vagotomy operation is an appropriate operation for almost all patients with chronic duodenal ulcer, if judged merely by the criterion that acid secretion of nearly all patients after this operation falls below the mean value of the normal population.[72] More radical surgical operations, such as partial gastrectomy with or without vagotomy, reduce acid secretion more effectively than the less radical operations of vagotomy and/or drainage, but we doubt if they are necessary and justifiable in view of their possible increased mortality and morbidity.[6]

Preoperative basal acid output and maximum acid output did not influence the postoperative incidence of recurrence or side effects after gastrojejunostomy[14] or partial gastrectomy.[68] For vagotomy and drainage operations the data are conflicting. In three British series[10, 13, 18] recurrent ulcer was equally common in the lower and upper halves of the range of preoperative maximum acid output. These British series are small and none of them can be compared with the 99 per cent follow-up study by Kronborg[54] of 500 patients 6 to 8 years after vagotomy and pyloroplasty. In this Copenhagen series, recurrent ulceration occurred at an unacceptably high rate of 21 per cent in that third of men with duodenal ulcer whose preoperative maximum acid output was more than 46 mmol per hr.

We suggest that the problem, whether preoperative acid studies are

of prognostic value, would be clarified if other centers published their data. To date, policies of selective surgery have not proved their usefulness, nor have there been prospective randomized trials of such policies. We believe that vagotomy is a suitable basic operation for patients with duodenal ulcer (except gastrinoma or antral G-Cell hyperplasia), whatever their acid status. It is possible that a more radical procedure should be selected as a first operation for patients with marked hypersecretion but data to decide this point have not been published.

When Johnston et al.[43] retrospectively compared the 2 to 5-year results of 40 hypersecretors (peak acid output after pentagastrin in men more than 50 mmol per hr, women more than 40 mmol per hr) and 60 normosecretors (peak acid output in men 30 to 50 mmol per hr, women 25 to 40 mmol per hr) the reductions in peak acid output after proximal gastric vagotomy were similar (52 per cent and 48 per cent), there were no proven recurrences in either group, and there was no significant difference between the incidence of postoperative symptoms. Obviously, since the whole series contained no recurrences it was not possible to compare the recurrence rates in the normosecretors and hypersecretors.

However, in the series with the highest published recurrence rate, 11 recurrences produced by seven surgeons in 50 patients, the mean preoperative peak acid outputs in the nine men with recurrence (45.1 mmol per hr) was similar to the 27 men without recurrence (49.2), and the preoperative peak acid output of the two women with recurrence (17.0 and 24.6 mmol per hr) was lower than the mean for the 12 women without recurrence (39.8 mmol per hr).[55]

9. Vagotomy Sequelae Are Due to Vagotomy

For decades all published series of the results of gastric operations recounted the incidence of nausea, vomiting, dumping, and diarrhea, and it has generally been assumed that these symptoms after vagotomy are due to the vagotomy, and do not exist in health.

Kennedy et al.,[50] in addition to their randomized control trial of 50 patients treated by proximal gastric vagotomy, and the 50 by selective vagotomy and gastrojejunostomy, interviewed a control group of 56 age- and sex-matched patients with no known gastrointestinal disease (Table 5). The incidence of miscellaneous "postvagotomy symptoms" was similar in the healthy controls and there was no significant difference in the Visick I (no symptoms) between the group of patients with duodenal ulcer who had been treated by proximal gastric vagotomy (60 per cent) and the healthy subjects (77 per cent). Thus with the exception of recurrent ulceration and bile vomiting, patients with proximal gastric vagotomy merely have a similar incidence of minor gastrointestinal symptoms to the control population.

Kennedy et al.[50] assessed their postvagotomy symptoms by interview, but Edwards et al.[25] measured fecal fat in a metabolic ward and found steatorrhea (> 6 gm per day) in five of 11 patients after truncal vagotomy and pyloroplasty, one of nine after selective vagotomy and pyloroplasty, one of nine after proximal gastric (highly selective) vagotomy *and* one of 16 patients with duodenal ulcer before any operation.

Table 5. *Incidence of Alimentary Symptoms in 50 Patients 1 to 4 Years After Proximal Gastric Vagotomy and in 86 Hospital Controls Without Gastrointestinal Symptoms (Kennedy et al.[50])*

	Proximal Gastric Vagotomy Per Cent	Hospital Controls Per Cent
Nausea	10	4
Food Vomiting	10	5
Bile Vomiting	2	0
Heartburn	14	18
Flatulence	18	13
Visick I	60	77
II	36	23
III	2	0
IV	2	0
I + II	96	100

10. Vagotomy Necessitates Drainage

Truncal. When Dragstedt first performed truncal vagotomy alone for duodenal ulcer he found that gastric retention was common. As a result, for the past 30 years the operation of truncal vagotomy has been accompanied by either gastrojejunostomy or pyloroplasty.

Selective. When selective vagotomy was introduced various groups tried again to avoid drainage procedure, but retention was once more a major problem,[26, 37, 67] as could be expected from the animal studies.[67] Burge et al.[11] remained more optimistic at first, but later accepted proximal gastric vagotomy as preferable. When Clarke et al.[17] tried selective vagotomy without drainage in 15 patients with duodenal ulcer, each developed gastric stasis, and three developed a gastric ulcer, two of whom required reoperation.

Proximal Gastric. When Holle and Hart[34] introduced selective proximal vagotomy they always added a drainage procedure or resection, and their group still does. The experimental evidence[2, 3] suggested that gastric stasis did not occur if antral innervation was preserved. As a consequence both Johnston and Wilkinson[44, 45] and Amdrup and Jensen[4] began their series without drainage procedures, and Hedenstedt[31] was also later able to omit pyloroplasty from his selective proximal vagotomy.[61] Moreover, the controlled trial of Wastell et al.[75] showed that the addition of pyloroplasty to proximal gastric vagotomy increased the incidence of epigastric fullness and dumping, and worsened the overall Visick I (perfect results) from 63 per cent to 36 per cent.

In our controlled study[48] of the gastric emptying of isotopically labelled meals, 1 month after operation patients who had undergone vagotomy and antrectomy had a significantly slower emptying than the control group. After 4 months this was returning towards normal, and by 6 months no difference between this group and the controls could be observed. At no stage did the patients treated by proximal gastric vagotomy show significant differences from the controls. These findings

correlated well with our clinical assessment 1 month after operation when 10 patients after antrectomy had moderate to severe symptoms of epigastric fullness, whereas this symptom was present in only five patients after proximal vagotomy, this difference being statistically significant. These symptoms abated later, as gastric emptying returned to normal.

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Selective, Highly Selective, or Truncal Vagotomy?

In 1976—A Clinical Appraisal

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The stomach is, first and foremost, a reservoir. It is a muscular bag, equipped with sphincters at either end: the cardiac sphincter prevents reflux of gastric content into the esophagus, while the pylorus, which is now acknowledged to be a true sphincter,[21] acts in concert with the antrum and proximal duodenum both to regulate gastric emptying and to prevent reflux of potentially injurious bile salts into the stomach. The muscular bag acts both as a "hopper," which receives and holds the meal by receptive relaxation of the body and fundus, and as a "mill" which grinds solid food into smooth chyme, suitable for digestion and absorption in the small intestine. The antrum is the mill of the stomach. By its terminal antral contraction the stomach is able to discriminate between solids and liquids, liquid chyme passing onwards, while solid food is retropelled into the body of the stomach to undergo further trituration.[7] Emptying of a meal from the stomach is thus a gradual and orderly process, controlled in large measure by the antropyloroduodenal segment, which is itself under the control of nerves and hormones.

All the standard operations for peptic ulcer destroy or severely impair these functions of the stomach. Both partial gastrectomy and vagotomy with antrectomy (V+A) remove the entire antrum and pylorus. Complete gastric vagotomy with a drainage procedure (V+D) destroys or bypasses the pyloric sphincter, destroys or bypasses the terminal antral contraction, and cuts the motor nerve supply to the antral mill. Thus V+D renders the stomach incontinent of liquids (when the patient is sitting or standing), and as a result side effects such as dumping or diarrhea may ensue.[11, 76] There is now much evidence that the antrum, pylorus and duodenum can be left completely intact in the course of operations for peptic ulcer, and that vagal denervation can be confined to the acid-secreting part of the stomach. If that is true, it follows that

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peptic ulcers can be cured with less risk to life, fewer side effects and fewer long-term metabolic sequelae than ever was possible in the past.

The operations of truncal, selective, and highly selective vagotomy have been used both in the treatment of patients with gastric ulcer and in the treatment of patients with duodenal ulcer. We will discuss the surgical treatment of duodenal ulceration first and then that of gastric ulceration.

DUODENAL ULCER

Definitions and Rationale of the Three Types of Vagotomy

In 1943, L. R. Dragstedt changed the course of gastric surgery by showing that *truncal vagotomy* abolished the gastric hypersecretion and inappropriate nocturnal acid secretion of patients with duodenal ulcer, with the result that their ulcers healed.[16] Truncal vagotomy (TV), combined either with a drainage procedure (D) or with an antrectomy (A), remains the most popular method of surgical treatment for duodenal ulcer. TV deprives not only the stomach, but also the liver, gallbladder, bile ducts, pancreas, small intestine, and half the large intestine of their parasympathetic nerve supply (Fig. 1). It must be complemented by a pyloroplasty (P) or gastrojejunostomy (GJ), because when used alone it weakens the propulsive power of the antral mill and produces gastric stasis.

Bilateral selective vagotomy (SV) also denervates the entire stomach, so that the addition of a drainage procedure (D) is still necessary (see Fig. 1). SV, which was introduced by Jackson and by Franksson (independently) in 1948, seemed a more logical procedure than TV, because vagal denervation was confined to the target organ, the stomach, while the hepatic and coeliac vagal fibres to the other viscera were

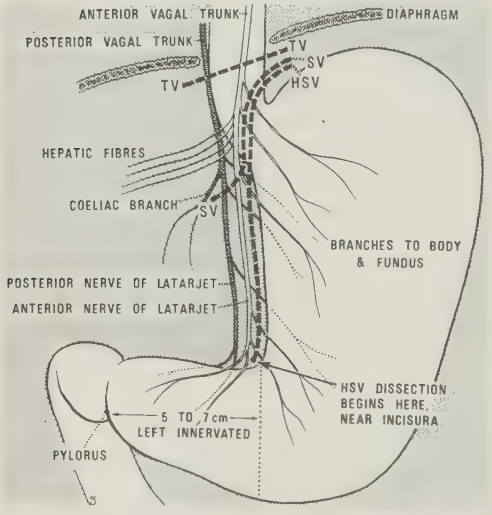

Figure 1. Distribution of the abdominal vagal nerves and lines of dissection for the three types of vagotomy (*TV*, truncal; *SV*, selective; *HSV*, highly selective). Note, however, that 5 or 6 cm of distal oesophagus must be cleared of all fibres at the end of each type of vagotomy.

preserved. The advocates of SV, such as Burge[5] and Griffith,[33, 34] claimed that SV+D gave clinical results superior to those of TV+D with respect both to recurrent ulceration and to side effects. They thought that recurrence would be less common after SV than after TV because the extragastric vagi were known to inhibit gastric secretion (in dogs),[62, 71] and because the meticulous technique which was needed for the performance of SV led to a more complete vagal denervation of the parietal cell mass. They also believed that small bowel, biliary, and pancreatic function would be better after SV than after TV and hence that side effects such as diarrhea would be reduced.

Highly selective vagotomy (HSV) is the first operation for peptic ulcer which both avoids gastric resection and keeps the antral mill and pyloric sphincter intact. In HSV, the vagal nerves (of Latarjet) to the antrum and the coeliac and the hepatic vagal fibres are all preserved. The procedure was first used in dogs by Griffith and Harkins in 1957[32] and in man by Amdrup and Jensen[1] and by Johnston and Wilkinson[56] in 1969. "Parietal cell vagotomy" (PCV), as used in Denmark by Amdrup and Jensen, differs slightly from HSV in that the precise extent of the antrum is "mapped" at the time of operation by means of a pH probe. HSV is a more empirical but simpler procedure in which careful inspection of anatomic landmarks is used to identify and preserve the nerves of Latarjet. "Selective proximal vagotomy" (SPV) antedated both HSV and PCV,[43] but was invariably accompanied by a pyloroplasty or antrectomy. The addition of a pyloroplasty to HSV/PCV has been shown to remove many of its advantages[10] and is, besides, unnecessary, either for efficient gastric emptying or for the achievement of satisfactory levels of gastrin or of acid. For these reasons, Amdrup and Johnston[4] have advocated the use of the term PCV for the operation if the antrum is mapped, and of HSV if it is not. For simplicity's sake in this review the term HSV will be used to cover both PCV and HSV.

The remainder of this article consists largely of a clinical comparison of these three types of vagotomy, but first a brief comparison of their physiologic effects is needed. We have had extensive experience of all three types of vagotomy in Leeds and have carried out studies of gastric secretion, serum gastrin, gastric emptying, biliary function, pancreatic function, and faecal fat secretion in patients who had regained good health, more than 1 year after TV, SV, or HSV. The groups of patients were carefully matched and each patient had been shown to have a complete vagotomy (of the parietal cell mass) by means of the Hollander insulin test soon after operation. All patients were followed up at yearly intervals at a special Gastric Follow-up Clinic, where they were interviewed by a panel of three physicians who did not know which operation had been performed until they had written down the answers to a standard set of questions and recorded their collective verdict according to a modified Visick system of grading.

Physiologic Comparison of the Three Types of Vagotomy

GASTRIN. All three types of vagotomy have been shown to produce a significant increase in serum gastrin.[36, 46, 88, 89] Gastrin levels are no higher when the antrum remains innervated than when it is vagally

denervated. Hence vagal release of gastrin seems to be relatively unimportant in man. These findings provide little support for the idea that recurrent ulceration will be common after HSV because the antrum is innervated.

GASTRIC SECRETION. Serial studies for up to 5 years after HSV have shown that reductions in basal and maximal acid output are little different from those found after TV or SV.[31, 47, 57, 58, 73] Only 3 per cent of the first 100 patients in Leeds had Hollander-positive insulin tests 1 week after operation, but serial testing for 5 years showed that 90 per cent of them eventually developed positive tests.[58, 73] However, the mean acid response to insulin was still reduced by 90 per cent, 5 years after operation. Approximately 50 per cent of patients have been found to develop positive insulin tests in the long term after TV or SV.[24, 68]

The inter-surgeon variation in ability to achieve a complete vagotomy, which we described previously after TV and SV,[55] has been found also after HSV. Many surgeons find that fewer than 10 per cent of their insulin tests are Hollander-positive 1 week after HSV, but others find that up to 58 per cent of the insulin tests are positive at this time.[70, 93] After TV, if the Hollander test is early-positive (in the first hour) 1 week after operation, the risk of recurrent ulceration is about 25 per cent; if late-positive, 10 per cent; and if negative, 2 per cent.[63] The risks of recurrence are probably similar after HSV. For example, in the series in which 58 per cent of Hollander tests were positive 1 week after HSV, 22 per cent of the patients developed recurrent ulceration within 1 to 4 years.[70] In contrast, only one of our first 100 patients has developed recurrent ulceration, after 4 to 7 years. We have found no correlation between positive Hollander tests 1 to 5 years after HSV, and recurrent ulceration. It is the insulin test 1 week after vagotomy which seems to have the greatest prognostic value.

DUODENOGASTRIC REFLUX AND GASTRITIS. Reflux of bile into the stomach, gastritis, and symptoms attributable to both of these, have been found to be considerably less after HSV than after either TV+P or TV+A.[61]

GASTRIC EMPTYING. HSV does not produce gastric stasis.[10, 50] Persisting stasis necessitating the addition of a drainage procedure occurred in only 0.8 per cent of 5539 patients after HSV.[50] All three types of vagotomy alter the pattern of gastric emptying, but the pattern is much closer to normal after HSV than after V+D.[10, 95] The presence of a pyloroplasty has been shown to exaggerate the abnormality of emptying which is produced by vagotomy.[10] When a hypertonic test meal was given orally to patients after either HSV or V+P, significantly more dumping, diarrhea, and hypotension ensued in patients who had undergone V+P than in patients who had undergone HSV.[45, 53]

GALLBLADDER. The gallbladder has been shown to dilate significantly in man after TV. After SV and HSV, it does not dilate.[80, 82]

PANCREAS AND SMALL INTESTINE.[48] The pancreatic enzyme response to insulin hypoglycemia is abolished by TV in man, but persists after SV and HSV. The insulin response to *oral* glucose was found to be double that to *intravenous* glucose in patients after SV and HSV,

whereas after TV the insulin response to oral glucose was no greater than the response to intravenous glucose. Hence the release of a small bowel hormone(s) which promotes insulin release after oral glucose may be impaired after TV. Other evidence suggests that the release of cholecystokinin from small bowel mucosa may also be impaired after truncal vagotomy.

Faecal Fat Excretion. This increases significantly after both TV+D and SV+D, whereas after HSV it is unchanged.[48]

Clinical Comparison of Truncal, Selective, and Highly Selective Vagotomy in the Elective Surgical Treatment of Duodenal Ulcer

An excellent, critical review of this topic has recently been published by Schrock.[85]

Truncal Vagotomy with a Drainage Procedure

The operative mortality of TV+D was found to be 0.8 per cent, in a previous review of 6490 elective cases,[13] and in this review of 2743 cases it was 0.6 per cent. The mean incidence of recurrent ulceration is 9 per cent, when a 90 per cent follow-up of patients is achieved for a minimum period of 5 years (Tables 1 and 2). A further 5 per cent of patients have bad results because of malfunction of the stoma, side effects of operation such as epigastric discomfort, diarrhea, dumping, or vomiting, or because they should never have been selected for operation in the first place: these last are the surgical "albatrosses," who are often found to be alcoholics or of unstable personality. Thus, overall, one patient in 100 will die after TV+D, and in the remainder, results are excellent in 47 per cent, good in 27 per cent (total, 74 per cent good or excellent), fair in 12 per cent, and poor in 14 per cent (Tables 1, 2, and 6). Similar conclusions were reached in Schrock's review of this topic.

Results may deteriorate still further in the very long term after TV+D. For example, when 255 patients were reviewed 15 to 22 years after TV+GJ,[96] weight loss and iron-deficiency anemia were found to be very common, and 7 per cent of patients had pulmonary tuberculosis, presumably because of malnutrition. Thus TV+D is by no means free from the long-term complications which we have come to expect after partial gastrectomy.

Choice of Drainage Procedure (TV+P or TV+GJ). Recurrent ulceration is commoner after TV+P, bilious vomiting after TV+GJ. The overall results of the two procedures are about the same (see Tables 1, 2, and 6).

Prospective Comparison of Truncal Vagotomy+Antrectomy (TV+A) With Truncal Vagotomy Plus a Drainage Procedure (TV+D). The incidence of recurrent ulceration after TV+A (1 per cent) is significantly less ($p < 0.01$) than the incidence of recurrence (9 per cent) after TV + D (Tables 3 and 6). Surprisingly, perhaps, side effects of operation were found to be little, if any, worse after TV+A than after TV+D. Hence overall results were better after TV+A (85 per cent good-excellent) than after TV+D (74 per cent good-excellent). Thus, provided that the use of V + A is avoided in high-risk patients or

Table 1. *Long-Term Results of Truncal Vagotomy*

	GOLIGHER ET AL.[25] LEEDS/YORK 1968	GOLIGHER ET AL.[25] LEEDS/YORK 1968	POSTLETHWAIT V.A. CO-OP. STUDY[81] 1973	COX[12] GLASGOW 1968	HOERR AND WARD[42] CLEVELAND CLINIC 1972
LENGTH OF FOLLOW-UP (YR)	5–8	5–8	5+	9	5–20
COMPLETENESS OF FOLLOW-UP (%)	97	92	85	83	90
SEX OF PATIENTS (M/F)	M	F	M	M	M+F
NUMBER OF PATIENTS	119	66	106	51	155
1. OPERATIVE MORTALITY (%)	0	0	0.6	1.3	0.7
2. RECURRENT ULCERATION* (%)	4	9	6	4	8
3. FUNCTIONAL RESULTS†					
GRADE 1. PERFECT (%)	44	28	Not clearly	Not clear	73(?)
GRADE 2. GOOD (%)	26 } 70	30 } 58	separated		
GRADE 3. FAIR (%)	19	20	from V-P		17(?)
GRADE 4. POOR (%)	11	22			10(?)

*"Proved" recurrent ulcer was scored: 1; "probable" or "highly suspicious": 1/3; lesser degrees of suspicion: 0. Recurrent duodenal ulcers, stomal ulcers, and gastric ulcers have all been classified as "recurrent" ulcers.

†These are the results *without* taking into account the beneficial effects of reoperation for recurrent ulcer; hence data quoted may differ somewhat from those in the original article.

Table 2. *Long-term Results of Truncal Vagotomy*

	GOLIGHER ET AL.[25] LEEDS/YORK 1968*	JORDAN[60] HOUSTON 1974*	T. L. KENNEDY ET AL.[65] BELFAST 1973*	POSTLE-THWAIT[81] V.A. CO-OP STUDY 1973*
LENGTH OF FOLLOW-UP (YR)	5–8	5–8	5	5+
COMPLETENESS OF FOLLOW-UP (%)	91	94	98	85
SEX OF PATIENTS (M/F)	M	M	M+F	M
NUMBER OF PATIENTS	164	106	46	135
1. OPERATIVE MORTALITY (%)	0.5	1.8	0	0.6
2. RECURRENT ULCERATION† (%)	8	8	7	9
3. FUNCTIONAL RESULTS				
GRADE 1. PERFECT (%)	45	70	63	Not
GRADE 2. GOOD (%)	23 } 68	14 } 84	24 } 87	clearly
GRADE 3. FAIR (%)	18	6	4	separated
GRADE 4. POOR (%)	14	10	9	from V+GJ

*TV+P performed as part of a prospective random trial.

†Recurrent ulcer, if "proved", scored 1; if "probable" or "strongly suspected", scored 1/3; and if more dubious, scored 0. Both recurrent duodenal ulcers and gastric ulcers have been classified as "recurrent" ulcers.

With Gastrojejunostomy for Duodenal Ulcer

FEGGETTER AND PRINGLE[20] NEWCASTLE 1963	WASTELL (N. TANNER)[92] LONDON 1969	NOBLES[79] MEMPHIS 1966	DELLIPIANI ET AL.[15] EDINBURGH 1969	WALTERS AND MOBLEY[91] MAYO CLINIC 1957	BURGE AND CLARK[6] LONDON 1960	DRAGSTEDT AND WOODWARD[17] CHICAGO 1951	F.KENNEDY ET AL.[63] GLASGOW 1973	HENSON AND ROB[41] LONDON 1955
10–14	10–20	15	5–10	5–10	9–12	1–7	2–6	2½
85	85	72	98	78	95	100	83	90
98%M	M+F	M+F	M+F	90%M	M+F	M+F	M+F	M+F
195	71	102	140	123	262	219	167	89
0.4	1.4	1.1	0.7	?	0	1.8	0.5	1
4	4	24	4	13	5	6	3	12
66 / 17 } 83	50 / 38 } 88	– / –	39 / 26 } 65	33 / 43 } 76	Not clear	} 81	} 86	37 / 10 } 47
8	3	–	24	9		10	7	34
9	9	–	11	15		9	7	19

and Pyloroplasty for Duodenal Ulcer

HOERR AND WARD[42] CLEVELAND CLINIC 1972	KRONBORG[69] COPENHAGEN 1975	BURGE AND CLARK[6] LONDON 1960	WASTELL (N.TANNER)[92] LONDON 1969	SMALL AND JAHADI[87] WORCESTER, MASS. 1970	F. KENNEDY ET AL.[63] GLASGOW 1973*	STEMPIEN ET AL.[90] LONG BEACH 1971
5–20	6–8	9–12	10–20	4–11	2–6	10–18
90	99	95	82	98	83	64
M+F	M+F	M+F	M+F	M+F	M+F	M+F
168	366	126	81	137	166	161
1.2	0.6	1.6	0	0.7	0	–
8	12	6	3	7	5	27
Not clear	46 / 26 } 72	Not clear	33 / 48 } 81	} 90	} 88	} 68
	6		9	3	5	} 32
	22		10	7	7	

Table 3. *Comparison of Results After Truncal Vagotomy With Antrectomy (TV-A) and Truncal Vagotomy With Drainage (TV-D)*

	(1) GOLIGHER ET AL.[25] LEEDS/YORK 1968		(2) JORDAN[60] HOUSTON 1974		(3) POSTLETHWAIT[81] V.A. CO-OP STUDY 1973		(4) HOERR AND WARD[42] CLEVELAND CLINIC 1972		(5) HOWARD ET AL.[44] MINNEAPOLIS 1973		WEIGHTED MEAN RESULTS	
	TV-A (BII)	TV-GJ	TV-A (BI)	TV-P*	TV-A (30%BI,70%BII)	TV-D	TV-A	TV-D	TV-A	TV-P	TV-A	TV-D
LENGTH OF FOLLOW-UP (YEARS)	5–8		5–8		5+		5–20		2–10		7	7
COMPLETENESS OF FOLLOW-UP (%)	96		94		85		90		?		90	90
SEX OF PATIENTS (M/F)	M		M		M		M+F		M		M	M
NUMBER OF PATIENTS	119	116	92	106	213	212	121	323	51	70	596	827
OPERATIVE MORTALITY (%)	0	0	0	1.8	0.9	0.6	3.9	1.0	0	0	1.0	0.7
RECURRENT ULCERATION (%)	1	4	1	8	1	8	2	8	4	10	1.3	7.6
FUNCTIONAL RESULTS:											' Mean of (1), (2), and (3)† n=424	n=434
GRADE 1. PERFECT (%)	50	44	58	70	52	45	No sig. diff.		No sig. diff.		53	51
GRADE 2. GOOD (%)	28 } 78	26 } 70	28 } 86	14 } 84	36 } 88	30 } 75					32 } 85	25 } 76
GRADE 3. FAIR (%)	14	19	10	6	9	15					10	14
GRADE 4. POOR (%)	8	11	4	10	3	10					5	10

*In Jordan's trial there were a few GJs.

BI, BII: Billroth I and II partial gastrectomy.

†Studies (1), (2), and (3) were prospective, randomized, controlled trials.

There were significantly more recurrent ulcers ($P < 0.01$) and significantly more poor results ($P < 0.01$) after TV-D than after TV-A.

when the duodenum poses technical problems, TV±A seems to give better overall results than TV+D. We think, in fact, that there is little to choose between the two procedures for the following reasons. First, recurrence is related to incompleteness of vagotomy, and many individual surgeons can keep their incomplete-vagotomy rate to less than 10 per cent,[55] which implies that the incidence of recurrent ulceration after TV+D in their hands is likely to be 6 per cent or less. Hence, antrectomy would be needless surgery in 94 per cent of their patients. Secondly, TV+A certainly has a higher operative mortality than TV+D, and if standards of technical surgery are less than superb one man more per 100 is liable to die after TV+A than after TV+D. Such an outcome would, in our opinion, cancel out the superiority of TV+A in terms of recurrent ulceration, and indeed would make TV+D the wiser choice, because side-effects and long-term effects are probably marginally less severe after TV+D than after TV+A. When one of us applied a "scoring system" to the outcome of the two procedures, the results were found to be almost identical.[49]

To sum up, truncal vagotomy with a drainage procedure has an operative mortality of 0.7 per cent, yields excellent or good results in only 73 per cent of patients (9 per cent develop recurrent ulceration), and has long-term sequelae which are far from negligible. Such results give no grounds for complacency. There is certainly room for improvement.

Selective Vagotomy with a Drainage Procedure

Like TV, SV cuts the main parasympathetic nerve supply to the antral mill. Although many patients have adequate gastric emptying after SV alone, many others develop gastric stasis and even gastric ulceration. Since it is impossible to predict before operation which patients will empty well and which will not, a drainage procedure should always be used.[8]

The advocates of SV claimed that, compared with TV, it ensured greater completeness of vagotomy (and hence a lower incidence of recurrent ulceration) and that it was followed by fewer side effects, diarrhea in particular. There is now much evidence to support these views.[65, 68] For example, in an excellent prospective random trial of TV+P versus SV+P , T. L. Kennedy et al. found significantly fewer incomplete vagotomies and significantly less diarrhea after SV than after TV.[65] There were also fewer recurrent ulcers after SV. However, despite these differences the overall clinical results after SV were not much better than those of TV, and some side effects of operation, early dumping in particular, were more common after SV than after TV (Table 5). In a similar trial in Copenhagen,[68] Kronborg et al. (1970) found that 40 per cent of vagotomies were incomplete after SV+P, whereas "only" 29 per cent were incomplete after TV+P. Not surprisingly, the incidence of recurrent ulceration was high (8 per cent) in both groups of patients, and the overall clinical results at 5 years were not significantly different. Diarrhea, however, was significantly less common after SV than after TV (see Table 5). In Leeds, the comparison between SV+D and TV+D was more open to criticism because patients were not allotted at random to

Table 4. *Long-Term Results of Selective Vagotomy With "Drainage" for Duodenal Ulcer*

	AMDRUP AND JENSEN[2] COPENHAGEN 1973 SV+P (HM)*	T. KENNEDY ET AL.[65] BELFAST 1973† SV+P (F)*	GRIFFITH ET AL.[34] SEATTLE 1972 SV+P (F)*	DE MIGUEL[14] VALLADOLID 1974 SV+P (F,HM)*	GOLIGHER ET AL. LEEDS (UNPUBLISHED) SV+D*	KRONBORG ET AL.[68] COPENHAGEN 1970† SV+P	KRONBORG AND MADSEN[70] COPENHAGEN 1975† SV+P (HM)*	T. KENNEDY ET AL.[66] BELFAST 1975† SV+GJ	GRASSI[28] ROME 1970 SV+GJ	SV+P
LENGTH OF FOLLOW-UP (YR)	5–8	5	4–9	5–9	5–8	5	1–4	1–4	0–7	0-7
COMPLETENESS OF FOLLOW-UP (%)	82	100	95	98	79	98	96	98	81	81
SEX OF PATIENTS (M/F)	M+F	M+F	M+F	M+F	M+F	M+F	M+F	M+F	M+F	M+F
NUMBER OF PATIENTS	100	50	103	131	92	38	50	50	114	376
OPERATIVE MORTALITY (%)	0	0	0.9	0	0.8	0	0	0	1	1
RECURRENT ULCERATIION‡ (%)	6	0	2	8	11	8	8	2	9	4
FUNCTIONAL RESULTS:										
GRADE 1. PERFECT (%)	55	55	–	60	37	71	40	33	–	–
GRADE 2. GOOD (%)	30 } 85	41 } 96	–	23 } 83	22 } 59	–	28 } 68	43 } 76	–	–
GRADE 3. FAIR (%)	5	0	–	8	21	–	24	18	–	–
GRADE 4. POOR (%)	10	4	–	9	20	–	8	6	–	–

*SV+P (F, HM): Bilateral selective vagotomy with Finney (F) or Heineke-Mikulicz (HM) pyloroplasty.
D: drainage procedure – 80 per cent, P, 20 per cent GJ in Leeds.
†SV+P performed as part of prospective, randomized, controlled trial.
‡Recurrent ulceration: duodenal, gastric, and stomal ulcers have all been included. "Proved" recurrence was counted as 1; "probable" or "strongly suspected" as 1/3, and more dubious as 0.

one or other procedure. However, for what they are worth, our results[75] provided no support for the idea that complete vagotomy is more certain with SV than with TV, recurrent ulceration was just as common, and the overall clinical results were no better. The clinical results after SV+D are summarized in Tables 4, 5, and 6.

The ability of individual surgeons to achieve a complete TV or SV (as judged by the finding of a Hollander-positive insulin test 1 week after operation) has been found to vary enormously, even among very experienced surgeons, some achieving a complete vagotomy of the parietal cell mass in almost every case, whereas others left 30, 40, or even 50 per cent of their patients with the vagotomy incomplete. It did not seem to matter whether the vagotomy was truncal or selective in type. Thus if the parietal cell mass is to be denervated effectively, it is the surgeon operating who matters, more than the particular type of vagotomy.[55]

To sum up, there is good evidence that selective vagotomy reduces the incidence of troublesome diarrhea significantly and there is some evidence that it reduces the incidence of incomplete vagotomy, but there is very little evidence that the overall clinical results after SV+D are significantly better than those of TV+D. Selective vagotomy shares with TV the disadvantage that a drainage procedure must be added. In our opinion, if in 1976 surgeons are going to take the trouble to perform a selective type of vagotomy, they would do better to perform a highly selective vagotomy, which possesses the added advantage of preserving the function of the antral mill and pylorus, and which yields considerably better clinical results.

Table 5. *Prospective Random Trials of Truncal and Selective Vagotomy*

	KENNEDY ET AL.[65] BELFAST, 1973		KRONBORG ET AL.[68] COPENHAGEN, 1970	
	TV+P	SV+P	TV+P	SV+P
NUMBER OF PATIENTS	50	50	38	38
LENGTH OF FOLLOW-UP (YR)	5	5	5	5
POSITIVE INSULIN TESTS* (%)				
1 WK AFTER OPERATION	18	4	29	40
RECURRENT ULCERATION (%)	7	0	8	8
DUMPING (%)	11	26	No significant difference	
DIARRHOEA† (%)	27	8	37	6
CLINICAL GRADING:				
1. PERFECT (%)	63	55	No significant difference	
2. GOOD (%)	24 } 87	41 } 96		
3. FAIR (%)	4	0		
4. POOR (%)	9	4		

*By Hollander's criteria.

†Diarrhoea is significantly less common after SV than after TV in both trials. Incomplete vagotomy was significantly less common after SV in the Belfast trial, but not in Copenhagen.

Table 6. *Mean Long-Term Results of Truncal Vagotomy With Antrectomy, Truncal Vagotomy With a Drainage Procedure; and Bilateral Selective Vagotomy With Drainage for Duodenal Ulcer.*

	1 TRUNCAL V-A	2=(4+5) TRUNCAL V-D	3 SELECTIVE V-D	4 TV-P	5 TV-GJ
MEAN LENGTH OF FOLLOW-UP (YR)	7 (5–20)	8 (5–20)	6 (5–9)	8	8
COMPLETENESS OF FOLLOW-UP (%)	90	90	92	90	90
NUMBER OF PATIENTS	596	2743	514	1353	1390
OPERATIVE MORTALITY (%)	1.0	0.6	0.7	0.75	0.5
RECURRENT ULCERATION* (%)	1.3	8.9	5.3	10.8	7.0
FUNCTIONAL RESULTS:†					
GRADE 1. PERFECT (%)	53	47	49	49	46
GRADE 2. GOOD (%)	32 } 85	27 } 74	29 } 78	26	28
GRADE 3. FAIR (%)	10	12	12	9	14
GRADE 4. POOR (%)	5	14	10	16	12

*Recurrence was scored 1 if proved; 1/3 if "probable" or "strongly suspected".

†These are the results *before* any reoperation; thus if patients needed reoperation, for recurrence or other cause, the result is graded as "poor".

Highly Selective Vagotomy Without a Drainage Procedure

The *operative mortality* in 5539 elective cases was 0.3 per cent.[50] This is significantly less ($p < 0.01$) than the 0.8 per cent operative mortality of TV+D, if it is permissible to compare the results of large collected series. Necrosis of the lesser curvature occurred in 10 patients (0.2 per cent) and caused death in 5(0.1 per cent).[50] Such necrosis is probably ischaemic in origin. Hence if a patient develops signs of peritonitis after HSV, prompt laparotomy is indicated.

SIDE EFFECTS. Our studies of matched groups of patients after the three types of vagotomy in Leeds,[3, 45, 53] and subsequent prospective controlled trials by others,[66, 70] have shown clearly that side effects of operation such as dumping, diarrhea, and bilious vomiting are significantly less common after HSV than after TV or SV with a drainage procedure (Tables 7 and 8). As stated previously, gastric stasis is rare after HSV and in consequence symptoms of gastric retention such as heartburn, flatulence, and vomiting are no more common after HSV than after V+D. The commonest side effect after HSV is a sensation of postprandial fullness, which is due to failure of receptive relaxation (and hence increased pressure) in the denervated body of the stomach,[95] but even this side effect is no more common than after TV or SV+D. Mild dumping can still occur after HSV, for the same reason, but the incidence of dumping is significantly less after HSV than after any of the standard operative procedures.[3, 45, 66, 70]

RESULTS OF HSV IN LEEDS (1969–1976). We have now performed approximately 330 elective HSVs for duodenal ulcer in Leeds. The series is virtually consecutive and follow-up of the patients is 94 per cent

Table 7. *Side Effects 2 Years After Truncal, Selective, and Highly Selective Vagotomy for Duodenal Ulcer in Leeds**

SYMPTOM	TV+GJ (n=110) PER CENT	TV+P (n=158) PER CENT	SV+D† (n=85) PER CENT	HSV (n=107) PER CENT
Diarrhoea	–	22	16	4
(Severe diarrhoea)	–	(2)	(2)	(0)
Early dumping	11	10	20	6
Bilious vomiting	16	11	7	5
Nausea	16	26	26	14
Epigastric fullness	28	47	38	33
Heartburn	15	18	14	17
Dysphagia	0	1	2	2

*A nonrandom comparison.

†All patients were male, except in the SV+D group, of whom 24 were female. SV+D = 68P, 17GJ.

Table 8. *Results of Prospective Trials of Selective and Highly Selective Vagotomy at 1 to 4 Years*

	KENNEDY ET AL.[66] BELFAST, 1975		KRONBORG AND MADSEN[70] COPENHAGEN, 1975	
	SV+GJ	HSV	SV+P	HSV
NUMBER OF PATIENTS	50	50	50	50
OPERATIVE MORTALITY (%)	0	0	0	0
POSITIVE INSULIN TESTS* (%) AT 1 WEEK	4	4	60	58
RECURRENT ULCERATION (%)	2	2	8	22
DUMPING† (%)	37	8	30	6
DIARRHOEA (%)	12	4	20	6
BILIOUS VOMITING (%)	14	2	14	4
WEIGHT GAIN (kg)	0.3	4.2	–	–
CLINICAL GRADING AT 1–4 YEARS:				
1. PERFECT (%)	33	60	40	68
2. GOOD (%)	43 } 76	36 } 96	28 } 68	10 } 78
3. FAIR (%)	18	2	24	2
4. POOR (%)	6	2	8	20

*Results judged by Hollander's criteria.

†Dumping, diarrhoea, and bilious vomiting were each significantly commoner after SV+D than after HSV.

complete. The indications for advising surgical treatment have not been relaxed since the era of V+D: that is, the patients nearly all have pain which is responding poorly to medical measures, keeping them awake at night, causing them to lose time from work, and generally making life a misery. In addition, many have suffered previous complications such as bleeding or perforation. An important question is when to add a drainage procedure to HSV. The answer is deduced from the patient's history, without recourse to sophisticated studies of gastric emptying. If the patient can eat three good meals a day during the remissions of pain, we find that his stomach empties satisfactorily after HSV. Obviously, if the clinical features of established pyloric stenosis are present, something more than a simple HSV must be done. However, we found that it was possible to treat about 90 per cent of all DU patients coming to surgery by HSV alone, by making the assumption that the stomach would continue to empty well after HSV without drainage if it had emptied well before operation—albeit in many cases through a scarred and somewhat narrowed duodenum. The treatment of the remaining 10 per cent of patients with established pyloric stenosis is described later.

RECURRENT ULCERATION. None of our 330 patients died after HSV. One hundred ten patients have now been followed for 4 to 7 years and only one of them has been proved to have a recurrent duodenal ulcer. It is interesting that he was one of the three patients out of the first 100 who had a positive insulin test 1 week after operation.[58] Among the remaining patients who have been followed for less than 4 years, two further cases of recurrent ulceration have been found (one duodenal and one gastric). Thus to date the incidence of proved recurrent ulceration is 1 per cent. A further 4 per cent of patients have complained at times of epigastric pain which raised the suspicion of recurrence. Each of these patients has been investigated by barium meal examination and gastroduodenoscopy, with negative results. Since recurrence of ulceration after TV and SV for DU is usually early, about half the recurrences appearing within 2 years, these results suggest that HSV as practiced in Leeds provides lasting cure of the ulcer. We think that this low recurrence rate is due to the low incidence of incomplete vagotomy, as shown by the Hollander test 1 week after operation. In such circumstances, the addition of an antrectomy is seldom needed. We have compared the results in hypersecretors (whose peak response to pentagastrin was more than 50 mEq per hr HC1 before operation) with the results in the remaining patients, and found that hypersecretors obtained just as good clinical results after HSV as did the other patients.[59]

The overall clinical results (Visick Grades) in male patients who were followed up for 4 to 7 years after HSV in Leeds are compared with the results 5 to 8 years after TV + D and SV + D in Table 9; 82 per cent of patients obtained good results (Visick Grades 1 and 2) after HSV, whereas only 68 to 70 per cent of patients achieved such results after TV + D, and 59 per cent after SV + D. The results were better after HSV for two reasons: first, side effects were significantly less, and second, the incidence of recurrent ulceration was lower.

In other centres, the results of HSV have varied from the excellent to the disastrous. In Copenhagen, for example, Amdrup and Jensen had

Table 9. *Clinical Results After Three Types of Vagotomy for Duodenal Ulcer in Leeds* (Without Incorporating the Results of Reoperation)*

	TRUNCAL V+GJ (n=119)	TRUNCAL V+P (n=164)	SELECTIVE V+D† (n=92)	HSV† (n=100)
Length of follow-up	(5–8 yr)	(5–8 yr)	(5–8 yr)	(4–7 yr)
Visick Grading	PER CENT	PER CENT	PER CENT	PER CENT
Perfect 1.	44	45	37	52
Very good 2.	26 } 70	23 } 68	22 } 59	30 } 82
Fair 3	19	18	21	10
Poor 4.	11	14	20	8

*A retrospective, nonrandom comparison.

†All the TVs were male; about a quarter of the SVs and HSVs were female. About 80 per cent of the drainage procedures with SV were P, the remainder being GJ.

results which were similar to ours.[3] There has certainly been widespread agreement that the operation is safe and that side effects are reduced. It is the question of recurrent ulceration which has provoked the controversy. Many groups have recorded recurrence rates of less than 5 per cent on short-to-medium term follow-up,[3, 29, 30, 37 39, 66, 72, 78] but others have found incidence of recurrence ranging up to 22 per cent.[70, 93] The discrepancy between the results from different centres is well illustrated by the results of two well-designed prospective controlled trials in which HSV was compared with SV+D (see Table 8). In both centres, it was found that side effects were significantly less after HSV than after SV+D, but whereas in one trial the incidence of recurrence after HSV was 2 per cent, in the other it was 22 per cent. In the trial with the 2 per cent incidence of recurrence, the incidence of incomplete vagotomy was 4 per cent, whereas in the trial with 22 per cent recurrence no fewer than 58 per cent of the Hollander tests were positive, 1 week after operation. In another centre where the Hollander test was positive in 28 per cent of patients 1 week after operation, the incidence of recurrent ulceration was 13 per cent.[93] Thus when vagotomy of the parietal cell mass is incomplete, recurrence is likely, and when it is complete, recurrence is rare. These conclusions are hardly surprising and fit well with what we know of the risks of recurrence after TV and SV.

HSV COMPARED WITH VAGOTOMY-ANTRECTOMY. The results of surgery for duodenal ulcer depend on four principal factors—the operative mortality, the side effects, the incidence of recurrent ulceration, and the long-term effects. HSV is safer, produces significantly fewer side effects, and seems certain to have fewer long-term sequelae than V+A. Recurrence of ulceration will be more frequent, however, after HSV (5 to 10 per cent) than after V+A (1 to 2 per cent). We think that this equation favors HSV as the initial procedure for duodenal ulcer. If the surgeon is an expert vagotomist, the incidence of recurrent ulceration after HSV should be about 5 per cent, and most of these failures

can be salvaged by subsequent antrectomy. We do not think it is wise to remove the antrum and pylorus unnecessarily in 90 to 95 per cent of patients.

Choice of Elective Operation for Chronic Duodenal Ulcer. The choice seems to lie between truncal vagotomy combined with a drainage procedure or antrectomy, on the one hand, and HSV on the other, because SV+D has been found to possess little advantage over TV+D.

We think that HSV is a better operation than TV+D, because it has a slightly lower operative mortality, it produces significantly fewer side effects, and it seems on present evidence to be just as likely to cure the ulcer. Such a conclusion is only justified, however, if the HSV is well done technically. Certainly the incidence of positive Hollander tests 1 week after HSV must be kept to less than 20 per cent. Hence we think that surgeons who use HSV should check its completeness either at operation, or by the insulin test 1 week later. We think that incomplete vagotomies are usually incomplete on the esophagus, because there is little difficulty in choosing the correct spot at which to begin the dissection near the incisura, about 6 cm from the pylorus,[51, 66] and between there and the cardia the vagotomy must be complete because the lesser curvature is separated completely from the lesser omentum. When training other surgeons to perform HSV, we have found that the difficulties usually arise on the esophagus, which should be mobilized so that three or four fingers can be passed behind it. It should then be cleared of all small fibres for a distance of at least 5 cm above the esophagogastric junction.[27, 48, 51]

Treatment of Duodenal Ulcer Complicated by Pyloric Stenosis

About 10 per cent of patients who come to elective operation for duodenal ulcer have obstruction at the gastric outlet, which leads to copious vomiting, succession splash, and slow emptying of barium. The stenosis is seldom in the pylorus itself, but is usually just distal to it. Finding that gastric emptying was not delayed after HSV in non-obstructing duodenal ulceration, and in the hope of preserving and making use of the compensatory mechanisms of muscular hypertrophy and increased peristalsis which the stomach develops to try to overcome the obstruction, one of us began in 1971 to treat patients with established pyloric stenosis by HSV plus digital dilatation of the stenosis through a gastrotomy.[54] A consecutive series of 23 patients with pyloric stenosis has been treated in this way by DJ's "team" in the past 5 years.[77] The results obtained are compared in Tables 10 and 11 with those obtained in 23 consecutive patients with pyloric stenosis who were treated by TV+D by JCG's "team.". Although two patients in the HSV group "re-stenosed", both did well after the addition of a pyloroplasty, and the eventual results after HSV with dilatation were a good deal better than the results after TV+D (Table 11). Similar encouraging results after HSV combined with a small duodenoplasty for pyloric stenosis have recently been reported by T. L. Kennedy.[67] We must admit that such

Table 10. *Comparison of Two Groups of Patients Who Were Treated Either by HSV or by TV+D for Pyloric Stenosis**

	HSV PLUS DILATATION (n=23)	TRUNCAL V+D† (n 23)
Age (years)	53.6 ± 2.1	53.2 ± 2.6
Sex (M:F)	14:9	16:7
Length of ulcer history (yr)	16.7 ± 2.3	13.6 ± 2.2
Peak acid output (PAO) to pentagastrin (mEq per hr)	40.9 ± 4.4	40.6 ± 8.3

*Data in Tables 10 and 11 taken from McMahon, M. J., Greenall, M. J., Johnston, D., and Goligher, J. C.[77]

†D, drainage procedure: 13 GJ. 10 P.

results surprised even ourselves, because in many of our patients the degree of stenosis was severe. We are well aware that in other sites, such as the urethra and esophagus, restenosis is the rule after a single dilatation, and we can only presume that preservation of the parasympathetic nerves (of Latarjet) to the antrum, plus the dilatation, ensured that the propulsive properties of the hypertrophied antral muscle in these patients were used to the full. Prospective, random comparison of HSV plus dilatation (or duodenoplasty) with TV+D in patients with pyloric stenosis would be of great interest. Meanwhile, these results suggest that the antral "mill" and pyloric sphincter can be kept intact in nearly all patients who come to elective surgery for duodenal ulcer, if the surgeon so desires.

Haemorrhage and Perforation

These complications of peptic ulceration are discussed elsewhere in this symposium. Here, we would merely record that we have treated 15 *carefully-selected* patients with perforated chronic DU by HSV plus suture, without a death; and 20 *selected* patients with severe haemorrhage from DU or GU by HSV plus under-running, also without mortality, and without rebleeding.[54]

Table 11. *Results of Operation for Pyloric Stenosis as Recorded by "Blind" Assessment at the Gastric Follow-Up Clinic**

CATEGORY	HSV PLUS DILATATION† (23 patients)	TRUNCAL V+D† (23 patients)
1. Perfect	18 (78%)	10 (44%)
1 + 2. Very good or perfect	22 (96%)	17 (74%)
3. Fair	1 (4%)	5 (22%)
4. Poor	0	1 (4%)

*Follow-up ranged from 6 months to 5 years.

†The results quoted incorporate the results of reoperation (two in each group).

GASTRIC ULCER

Combined Gastric and Duodenal Ulceration

Such patients usually have patterns of gastric secretion similar to those of patients with duodenal ulcer, and treatment by some form of vagotomy as for duodenal ulcer alone has been found by most authors (including ourselves) to give good results.[64, 94] Some authors, however, report unacceptably high recurrence rates after vagotomy and recommend the use of vagotomy plus hemigastrectomy, with resection of both ulcers.[9]

Gastric Ulcer Alone

The evidence for and against the use of vagotomy for gastric ulcer has been reviewed by Forrest[22] and by Duthie.[18] Vagotomy has been advocated on the grounds that it is safer than partial gastrectomy (PG), but the evidence for this is meager, the mean mortality of V+D being about 1.4 per cent and of PG, about 1.8 per cent. Vagotomy has been claimed to be as effective as PG in curing the ulcer, but this is almost certainly not true, because the mean incidence of recurrent ulceration after PG is about 2 per cent, whereas after V+D it is about 5 per cent and can be as high as 19 per cent. The use of PG may lead to cure of an early ulcer-cancer, whereas there is a small but definite risk of missing an eminently curable cancer when V+D is used. This risk can be almost eliminated, however, by the use of multiple preoperative endoscopic biopsies, supplemented by further frozen-section biopsies (or complete excision of the ulcer) at the time of operation. Finally, there is little evidence that the side effects of V+D are less than those of Billroth I PG, and in Duthie and Kwong's prospective controlled trial[19] of V+P versus B-I PG, only 68 per cent of patients were found to be in Visick Grades 1 or 2 (good to excellent) at 5 years, whereas 78 per cent of patients were in Visick Grades 1 or 2 after B-I PG. Hence, we believe that Billroth I PG remains the treatment of choice for most patients with gastric ulcer.

There are special circumstances, however, in which vagotomy is probably preferable to gastrectomy. For example, in massive haemorrhage from gastric ulcer, the mortality of V+D plus under-running the bleeding vessel with nonabsorbable sutures is about half that of partial gastrectomy, while the incidence of re-bleeding is no greater.[9, 23, 40, 84] Again, when the ulcer is situated high on the lesser curve, or is present in a frail and elderly patient, it may be safer and wiser to perform V+D plus excision or biopsy of the ulcer, rather than PG.[9]

While the results of B-I are good, they are probably not as good as many people imagine. The operative mortality is 2 per cent. Only 78 per cent of Duthie and Kwong's patients were in Visick Grades 1 + 2, 5 years after B-I PG and unpublished data from Leeds and York (Goligher, Pulvertaft, Hall, Hopton, and Matheson) show that only about 74 per cent of patients were in Visick Grades 1 + 2, between 2 and 10 years after B-I PG. Thus we think that there is still room for improvement, and that both the pylorus-preserving gastrectomy of Maki[74] and HSV[38, 52] are worthy of trial.

One of us (DJ) has used HSV in the treatment of patients with gastric ulcer since 1969, and recorded encouraging early results in a small series of cases in 1972.[52] We have now treated 80 patients by HSV, of whom approximately two-thirds had gastric ulcer alone and one-third, combined gastric and duodenal ulceration. The series was not quite consecutive because a few patients were excluded on account of anticipated technical difficulties, suspicion that the ulcer was malignant, or because of the patient's poor general condition. Every effort was made to ensure that only benign ulcers were treated in this way and in fact, so far as we are aware, no case of early cancer has been missed. When the ulcer was close to the pylorus, or very large or inaccessible, it was not excised in toto but large biopsies were taken.

There was one operative death after HSV (1.2 per cent). Tests of gastric secretion, before and more than 1 year after operation, showed that basal acid output was abolished, that the response to pentagastrin was reduced by 80 per cent and, perhaps most important, that there was virtually no response to a test meal of meat extract after operation (M. Greenall, unpublished). Most of these patients have had follow-up barium meal examinations and no evidence of gastric stasis or recurrent ulceration has been found. Faecal fat excretion has been found to be significantly less than after B-I PG. Patients after HSV could eat bigger meals, and experienced less dumping, than patients who had undergone B-I PG for gastric ulcer. We emphasize that we are not yet in a position to advocate the widespread use of HSV in the treatment of patients with gastric ulcer, because the maximum period of follow-up is only 6½ years, and the mean is less than 3 years. Moreover, HSV for gastric ulcer is a difficult operation technically, and indeed at times is impossible to perform. However, our results to date are certainly encouraging. If HSV does prove in the long run to provide effective cure for gastric ulcer, we think that it will do so for two main reasons: first, because it greatly reduces acid and pepsin output, and second, because by raising intragastric pressure and speeding gastric emptying of liquids,[10, 95] it tends to prevent antral stasis and has been shown to reduce reflux of duodenal content into the stomach.[61]

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Truncal Vagotomy with Antrectomy — 1976

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Partial and complete truncal vagotomy combined with gastric resection of varying extent was sporadically used for the treatment of the complications of duodenal ulcer during the 1920's and 1930's.[36, 43] However, it remained for Farmer and Smithwick of Boston.[7, 8] and Edwards and Herrington[6] of Nashville to develop the physiologic operation of truncal vagotomy with conservative distal resection in the patient with duodenal ulcer. It has been well documented by Dragstedt[5] that division of the vagus nerves eliminates the cephalic phase of gastric secretion which comprises approximately 60 to 70 per cent of the acid output in the duodenal ulcer patient. Also, excision of the distal 40 to 50 per cent of the stomach removes the main source of the hormone *gastrin* which is responsible for the humoral phase of gastric secretion.

Late in 1946 Smithwick performed a bilateral truncal vagotomy with an estimated 50 per cent resection of the distal stomach for treatment of a patient who had developed a marginal ulcer following simple gastroenterostomy. He termed the distal resection a *hemigastrectomy.* Following resection Smithwick reconstructed the gastrointestinal tract using a retrocolic Hofmeister type gastrojejunostomy. In contrast, Edwards removed an estimated 40 per cent of the distal stomach along with diversion of the two main vagal trunks at the esophageal hiatus and termed the limited resection an *antrectomy.* He reconstructed the gastrointestinal tract with classic Billroth II type anastomosis. Both observers felt that this operative method represented a physiologic approach to the treatment of duodenal ulcer, eliminating both cephalic and humoral phases of gastric secretion but leaving the patient with a sizeable gastric reservoir. Subsequent secretory studies revealed a negative response to insulin hypoglycemia in the vast majority of patients and over 95 per cent had no free hydrochloric acid response to histamine or Betazole. In later years when more sophisticated gastric secretory studies became available it was found that the combined procedure resulted in a basal acid output (BAO) which was negligible and the peak acid output (PAO) following Betazole stimulation averaged between 1 to

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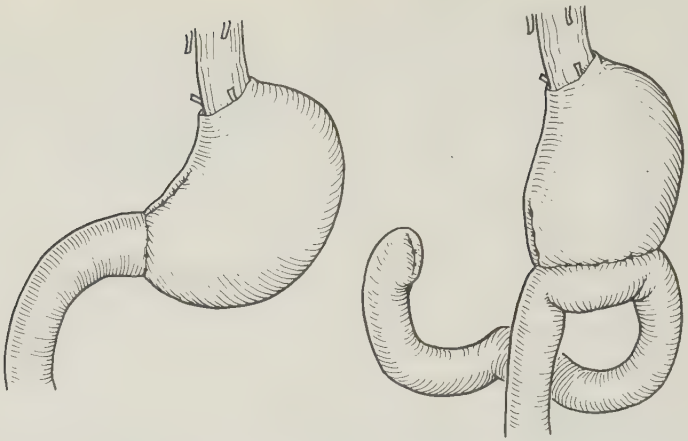

Figure 1. Left, Truncal vagotomy-antrectomy with end-to-end gastroduodenostomy. The Schoemaker method was utilized in excising and closing the lesser gastric curve. Right, Truncal vagotomy-antrectomy with left-to-right Hofmeister reconstruction.

3 mEq per hr. Twelve hour gastric secretory volumes were usually less than 200 milliliters. In more recent years it has been shown that serum gastrin levels are reduced appreciably following the procedure.

The operation of vagotomy-antrectomy has been the most frequently employed operation for the treatment of duodenal ulcer on the services of Vanderbilt University Hospital, St. Thomas Hospital, and Metropolitan General Hospital in Nashville during the past 27 years.[20] During the period from January 1946 through December 1974 our group has performed the combined operation on a total of 3771 patients. The ratio of men to women has been 5 to 1, the youngest patient was 8 years of age, and the oldest patient was 94 years of age. The average patient age has been 47 years and the length of ulcer history prior to surgical intervention averaged 12 years (Fig. 1).

Indications for operation among this group of patients have been those of chronic duodenal ulcer and its complications. Many patients had various combinations of indications, but the principal indication for operation in 51 per cent was recurrent ulcer pain refractory to medical management. A single life-threatening hemorrhage or repeated hemorrhage of lesser magnitude was the indication in 32 per cent of patients. Fourteen per cent of patients had gastric outflow tract obstruction and 3 per cent who were deemed good risks underwent the procedure for an acute ulcer perforation (Table 1).

Of the 3771 patients the follow-up has been complete in 98 per cent, thus 74 patients have been lost to follow-up (3697 patients followed). Some patients, of course, have subsequently died of unrelated causes over the longer range study, particularly those operated upon during the first 10 years. Each patient, however, was followed to the time of death and the results have continued to be tabulated in the long-range clinical study. The follow-up protocol has consisted of frequent office and hospital outpatient visits, hospital readmissions when necessary, and interviews by members of the surgical group. In many instances postoperative gastro-

Table 1. *Indications for Operation*

Refractory pain	51 per cent
Hemorrhage	32 per cent
Outlet obstruction	14 per cent
Perforation	3 per cent
	100 per cent

intestinal x-ray studies have been done, and in recent years fiberoptic endoscopy has been performed on any patient who returns with upper gastrointestinal symptoms which are considered significant. Postoperative gastric secretory data were obtained during the first 10 to 15 years of the study, and it was found that the early reduced secretory rates have remained markedly suppressed over this long interval of time.

Clinical results have been tabulated as excellent, good, fair, or poor. An excellent result indicates that the patient is in excellent nutritional condition and has no symptoms referable to the gastrointestinal tract. A good result is assigned those patients with no ulcer-like symptoms but who note epigastric fullness, mild to moderate dumping, and occasional bouts of diarrhea. A fair result is listed if the patient has obtained benefit from the operation but if significant postgastrectomy symptoms develop. A poor result indicates the patient who develops nutritional deficits, appreciable postgastrectomy symptoms, or a recurrent ulcer. Our results indicate that 66 per cent of patients have obtained an excellent clinical result and are free of gastrectomy sequelae. Twenty-eight per cent of patients have obtained a good result, 5 per cent a poor result, and failures have occurred in 1 per cent of patients (Table 2).

Weight loss after operation has not constituted a troublesome problem. Only 10 per cent of patients have experienced weight loss sufficient to cause concern and anemias have only occurred infrequently.

During the first 10 years of the study a Billroth II type of reconstruction was used exclusively. However, after the Billroth I method of reconstruction was repopularized in this country by Henry Harkins during the early 1950's, we gradually shifted to this method and have now used it almost exclusively for the past 15 years.

Symptoms of the dumping syndrome have occurred in 25 per cent of the series. This complication has been equally distributed between the Billroth I and Billroth II reconstructions, and in most instances the symptomatology has been mild to moderate in degree. In 10 to 15 per cent of patients some change in bowel habit has occurred, with most of

Table 2. *Results*

Excellent	66 per cent
Good	28 per cent
Poor	5 per cent
Failure	1 per cent
	100 per cent

this group experiencing 2 to 4 loose or semi-firm stools daily. In 1 per cent of patients diarrhea has been severe and disabling, and several of these patients have undergone remedial operations.

Among the entire group of patients 55 postoperative deaths occurred either in the hospital or within 30 days following operation (mortality of 1.4 per cent). The majority of deaths occurred in patients undergoing an emergency operation for control of massive bleeding. Most of these patients were elderly and had cardiovascular or renal disease. Pre-existing chronic respiratory problems accounted for death in several patients. Twelve patients died as a result of a duodenal stump blow out and all of these deaths occurred during the first 10 years when we were using the Billroth II method exclusively. Three patients died of overwhelming acute hemorrhagic pancreatitis during the early postoperative period and two deaths occurred as a result of repeated uncontrollable bleeding. It is of interest that our overall mortality has dropped from 3.1 per cent in 1958 to 1.4 per cent in 1974. Currently the mortality for the patient undergoing elective vagotomy-antrectomy is less than 1 per cent. The overall death rate from massive hemorrhage has been 3 per cent and the mortality for hemorrhage in the patient over age 60 has been 6 per cent.

The recurrent ulcer rate among the 3697 patients has been extremely low (0.5 per cent). Only 20 proven recurrent ulcers have taken place and we are not aware of any suspected cases of recurrence. Approximately 1600 patients have now been followed from 10 to 15 years. It is of extreme interest that each of the 20 recurrent ulcers became manifest by the presence of recurrent ulcer-like pain, bleeding, or perforation, each of these complications taking place within 24 months after vagotomy-antrectomy. This has been the experience of Farmer, Smithwick, and others as recurrent ulceration has apparently not taken place during the long range follow-up after vagotomy-antrectomy. The cause for recurrence in most of the 20 patients in our series was an incomplete vagotomy which was later proven by secretory testing or at reoperation. A Zollinger-Ellison tumor was responsible for recurrence in four patients and a functioning adrenal tumor caused a recurrent ulcer in one patient. Of the 20 recurrences, 13 followed vagotomy-antrectomy with a Billroth I reconstruction and seven recurrences took place after Billroth II type reconstruction. It should be emphasized, however, that during the past 15 years the Billroth I method has been used almost exclusively and it is seldom that we now perform a Billroth II type reconstruction. Even in most patients with a severe posterior penetrating ulcer the Billroth I method is utilized. It should be stressed, however, that when we first embarked on the Billroth I reconstruction (end-to-end gastroduodenostomy) we proceeded cautiously and only used the method when dealing with small duodenal ulcers in which there was minimal scarring about the periduodenal area. As experience increased we gradually began to apply the method to the more difficult ulcers, and when sufficient experience had accumulated we began to carry out end-to-end gastroduodenostomy on the majority of the deep posterior penetrating ulcers. We have not made it a point to excise the ulcer in every case, and in many instances have left a deep posterior penetrating ulcer

attached to the head of the pancreas and simply fashioned a cuff of duodenum distal to the ulcer to be used for the gastroduodenal anastomosis. With ulcers, however, which are massively bleeding at the time of operation, either the ulcer crater is obliterated or the ulcer totally removed. When the ulcer is left behind we have not hesitated to perform a Billroth I reconstruction being aware that some surgeons under such circumstances prefer to close the duodenal stump and utilize the Billroth II method. Currently, we are performing the Billroth I reconstruction in over 95 per cent of cases, and reserve the Billroth II method for the deep posterior penetrating ulcer in the patient who is extremely obese where technical considerations preclude end-to-end gastroduodenostomy. Also in patients with presenting symptoms of retrobulbar ulcer, where there is marked narrowing and stenosis of the retrobulbar duodenum, the Billroth II method is employed.

In the small percentage of patients in whom we elect to perform a Billroth II type reconstruction our preference is a retrocolic Hofmeister type anastomosis. We employ a very short afferent loop of jejunum measuring approximately 6 to 8 centimeters in the reconstruction. This short or practically no loop gastroenterostomy is most always placed in a left-to-right direction, suturing the afferent limb to the greater gastric curve and the efferent limb to the lesser curve. In a small number of patients, usually 5 per cent or less, where the ligament of Trietz lies to the right of the midline, we prefer a right-to-left anastomosis placing the afferent jejunal limb to the lesser gastric curve and the efferent limb to the greater curve. Care is taken to suture the gastric remnant to the periphery of the rent in the transverse mesocolon with interrupted silk sutures. The afferent and efferent limbs of jejunum just distal to the gastroenteric stoma are sutured to the posterior parietes to prevent angulation, twisting, or an internal hernia.

OPERATIVE TECHNIQUE

We have not altered our operative technique appreciably in recent years.[19, 21, 37] In performing bilateral truncal vagotomy it is our feeling that better exposure is obtained by dividing the suspensory ligament of the left lobe of the liver and retracting the left lobe to the right. Currently, some surgeons prefer to simply elevate the left hepatic lobe superiorly without dividing the suspensory ligament. The abdominal esophagus is gently mobilized with the operator's right index finger keeping the dissection deep to the posterior wall of the esophagus and close to the overlying aorta. This prevents injury to the esophageal wall. The right (posterior) vagal nerve trunk is first identified, freed up, and a generous length of this nerve (approximately 3 centimeters) is removed. The cut ends of the nerve are either tied with silk or stapled with metal clips. The left (anterior) vagus nerve is best freed up by exerting general downward traction on the gastrohepatic omentum near the gastroesophageal junction using the fingers of the left hand. This renders the left nerve taut and it can easily be freed up from its embedment in the anterior esophageal wall with the operator's right index

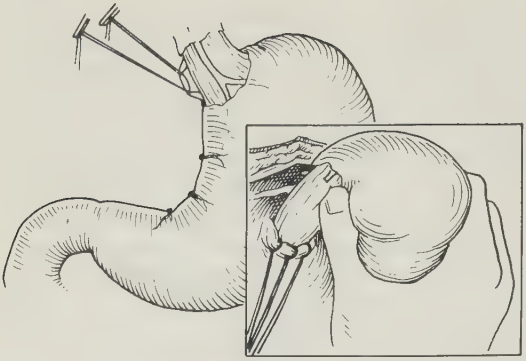

Figure 2. The anatomic location of the right and left vagal nerve. After completing the vagotomy the right crural sling is approximated if it is attenuated.

finger. A similar length segment is excised from this nerve. Any small nerve fibrils lying about the periesophageal area or along the longitudinal musculature of the esophageal wall can be divided with a fine knife blade. No attempt is made to approximate the peritoneum over the esophagus and the left lobe of the liver is allowed to fall back into its normal anatomic location (Fig. 2).

At this point we next free up the greater gastric curve keeping the dissection within the arterial arcade as close to the stomach wall as possible. The gastroepiploic vessels are freed from approximately the midportion of the greater curve distally to the pylorus. The gastrohepatic omentum is then divided and transfixed along the lesser curve approximately 2 to 3 centimeters above the angularis. Next we divide the greater gastric curve between Glassman clamps and apply an additional pair of clamps directed toward the lesser curve making bisection of the stomach (Fig. 3). The lesser curve aspect of the gastric pouch is closed beneath the Glassman clamp with a running suture of fine chromic catgut. A second row of interrupted 2-0 silk sutures are then placed after which the original running catgut suture is returned as a Lembert suture inverting the anterior and posterior gastric walls of the lesser curve. The antrum of the stomach or the distal estimated 40 per cent is

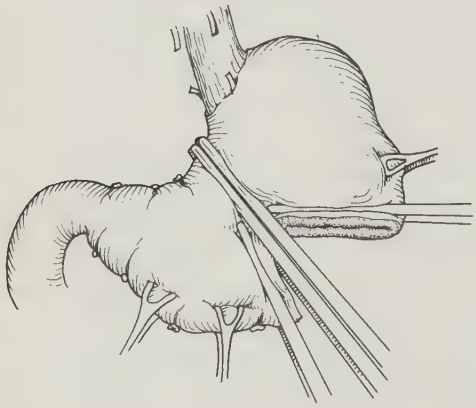

Figure 3. The greater gastric curve is divided at its midpoint between Glassman clamps. The proximal Glassman clamp defines the point at which the greater gastric curve will be anastomosed to the duodenum. Additional clamps are placed obliquely toward the lesser curve and the stomach will be divided between these clamps.

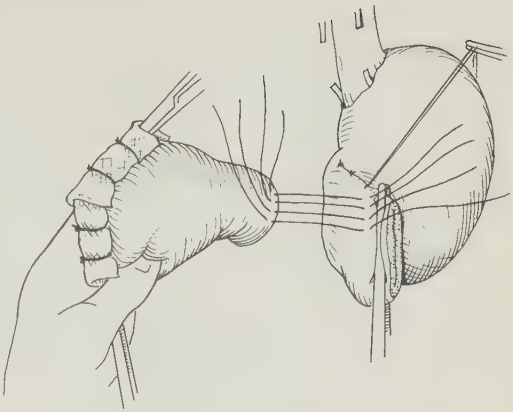

Figure 4. The antrum of the stomach has been transected and reflected to the right, and it serves as a handle for dissecting the periduodenal area. A posterior layer of seromuscular sutures is shown being placed between the posterior wall of the greater gastric curve and the posterior wall of the duodenum.

next reflected to the right and the right gastric and right gastroepiploic vessels are doubly clamped, divided, and transfixed. The dissection is taken past the pyloric sphincter. The use of the antrum of the stomach as a handle facilitates the dissection about the ulcer. The greater curve aspect of the gastric pouch is next placed in opposition to the first portion of the duodenum and the posterior wall of the gastric pouch is approximated to the posterior wall of the first portion of the duodenum using interrupted fine silk sutures (Fig. 4). The sutures are first placed after which the first assistant brings the greater curve of the gastric pouch in close opposition to the posterior wall of the duodenum. The interrupted silk sutures are then individually tied (Fig. 5). The antrum of the stomach and the proximal duodenum are next extirpated. The Glassman clamp is released from the greater curve of the gastric remnant and the gastroduodenal anastomosis is further accomplished by the use of a running posterior layer of fine catgut which encompasses the full thickness of the posterior wall of the gastric remnant and the full thickness of the posterior duodenal wall. The suture is then returned anteriorly as an inverting type stitch (Fig. 6). An outer layer of interrupted 4-0 silk completes the anastomosis. Care is taken to use a triangular suture at the lesser curve of the anastomosis which encompasses both the

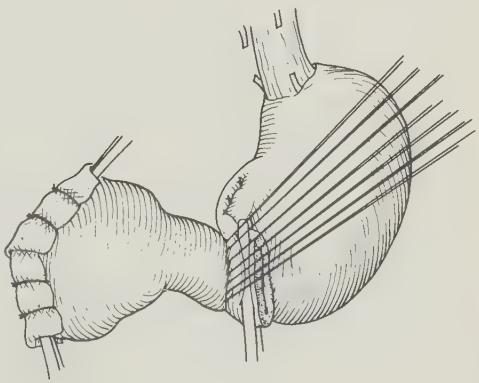

Figure 5. The gastric remnant is approximated to the posterior wall of the duodenum, and in the interrupted posterior layer of seromuscular sutures the sutures are individually tied.

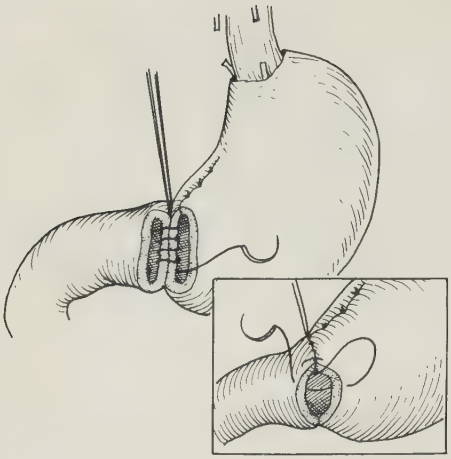

Figure 6. The gastric antrum and first portion of the duodenum have been removed. The Glassman clamp has been released from the greater gastric curve and the gastroduodenal anastomosis is further accomplished using a posterior continuous suture of fine catgut which includes the full thickness of both the gastric and duodenal walls. (*Insert*) This continuous suture is then advanced anteriorly as an inverting stitch.

anterior and posterior gastric walls as well as the lesser curve of the duodenum. This suture closes the potential weak spot in the anastomosis which has been referred to as the angle of sorrow (Jammerecke) (Fig. 7).

DISCUSSION

During the past quarter century literally thousands of cases of vagotomy-antrectomy have been performed throughout the surgical world. Unquestionably the combined procedure has stood the test of time and accumulated data show it to be associated with the smallest incidence of recurrent ulceration of any procedures in current use for treatment of duodenal ulcer. Among 589 patients, many of whom have been followed from 10 to 15 years, Farmer et al.[9] reported a recurrent ulcer rate of 1.5 per cent. Thoroughman et al.[41] cited a recurrent ulcer rate of 0.4 per cent over a 14-year follow-up. Wolf et al.[44] in reporting 547 patients cited a recurrence rate of 0.6 per cent during a 10-year follow-up. In Palumbo and Sharpe's series[38] of 611 patients undergoing distal antrectomy and

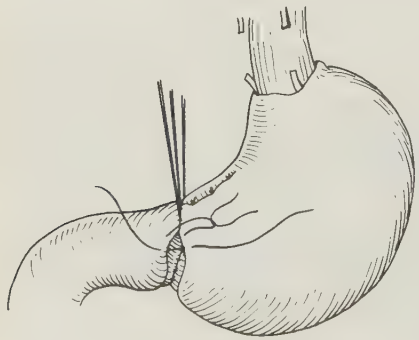

Figure 7. The anastomosis is completed with an outer layer of interrupted seromuscular silk sutures. Care is taken to close the angle at the lesser curve with one triangular suture.

vagotomy, a recurrence rate of 0.6 per cent was tabulated among 597 patients followed. Without exception all surgeons who have had experience with vagotomy-antrectomy acknowledge this remarkably low rate of recurrent ulceration and even the critics of the combined procedure acknowledge this fact. Over the years the main criticism of vagotomy-antrectomy has been the operative mortality which varies from 1 per cent in experienced hands up to 5 per cent among those with less experience. Jordan and Condon[31] rightfully stressed that vagotomy-antrectomy could be performed with a mortality rate comparable to that of a lesser procedure if extremely high risk patients were excluded. This decidedly has been our experience over the years and as stated we perform the combined procedure in 95 per cent or more of our patients and reserve operations of lesser magnitude for the elderly high risk individual.

There is no question but that truncal vagotomy-pyloroplasty is currently the most widely used operation throughout America to control the complications of duodenal ulcer. The advocates of this procedure stress the low operative mortality (less than 1 per cent in elective cases) and technical simplicity.[4, 10, 12] The recurrent ulcer rate, however, varies from 3 per cent to 30 per cent with most reports citing a recurrent ulcer rate of 10 to 15 per cent. The advocates[14, 22, 40] of truncal vagotomy-pyloroplasty, however, fail to appreciate that the 10 to 15 per cent of patients who do develop recurrent ulceration, not infrequently have massive bleeding or acute perforation, and reoperation for control of these complications under such circumstances is often associated with a mortality in the range of 5 per cent or more. Thus the mortality of 1 per cent or less following the initial operation of truncal vagotomy-pyloroplasty does not reveal the entire story. It is undeniable that the mortality and morbidity following re-operation for ulcer recurrence is directly related to the original procedure. This is not to say that truncal vagotomy-pyloroplasty has no place in the treatment of the complications of ulcer disease. In our opinion it has definite value as a compromise operation when faced with a severe posterior penetrating ulcer that does not lend itself to resection and when one encounters the elderly poor risk individual who will not tolerate an operation of greater magnitude.

Gastric selective vagotomy-pyloroplasty has been used by only a few groups in America[15, 39] but the procedure is widely used throughout Europe and the British Isles.[12] The mortality rate following this operation is comparable to that of truncal vagotomy-pyloroplasty but the recurrent ulcer rate is much less, varying from 3 to 10 per cent with most observers noting a recurrent ulcer rate in the range of 6 to 8 per cent. Studies have shown that gastric selective vagotomy results in a much lower incidence of positive insulin responses than does truncal vagotomy. This probably does not result from the fact that a more complete technical vagotomy is achieved with the gastric selective technique. Currently many observers speculate that the negative Hollander test may in part result from a humoral mechanism originating from the midgut which inhibits the gastric antrum.[15] It is possible that the VIP and the GIP hormones may play a role, as it is known that these agents are potent gastric antisecretagogues.

In recent years considerable excitement has arisen regarding the operation of proximal gastric vagotomy or parietal cell vagotomy. This procedure denervates only the parietal cell mass of the stomach while maintaining innervation to the antral pump, the gallbladder, common duct, pancreas, small intestine, and right half of the colon. Theoretically, at least, with the pylorus and antral pump left undisturbed and with vagal innervation to adjacent viscera maintained, the likelihood of postgastrectomy sequelae should be absent or diminished considerably. It is of extreme interest that this procedure is by no means a recent concept. It was conceived and reported experimentally in 1957 by Charles Griffith and the late Henry Harkins.[16] When they performed the operation on the experimental animal they found that gastric secretory activity was lowered appreciably and gastric motility and gastric emptying were almost comparable to that of the control animals. These observers, however, never employed the operation on a clinical basis. It remained for Hart and Holle of Munich in the early 1960's to perform the procedure on man. These observers over the ensuing years have amassed a large amount of clinical material but have elected to combine the operation with a pyloroplasty. Their results have been reported as excellent.[18, 23, 24]

During the past 8 years Amdrup and his group and Goligher, Wilkinson, and Johnston have reported encouraging preliminary results using parietal cell vagotomy without drainage. These observers[1-3, 13, 28, 30, 34] have now operated upon approximately 600 patients with near zero mortality and with excellent overall results. The dumping syndrome has not been completely eliminated, but has been reduced to approximately 5 per cent with no severe case of dumping occurring. Diarrhea also has not been completely eliminated, but no case of severe diarrhea has occurred.

Recently Johnston[29] in a worldwide survey of results with over 5000 parietal cell vagotomies performed electively without drainage for duodenal ulcer recorded a mortality rate of 0.3 per cent. The side effects of early dumping, bilious vomiting, and diarrhea have been lowered appreciably in comparison to other standard operations for ulcer. It is Johnston's current opinion that parietal cell vagotomy is probably the safest operation for duodenal ulcer, because the alimentary tract is not violated and there is no suture line or anastomosis to contend with. The operation appears from preliminary studies to be particularly applicable to the patient undergoing an elective operation for intractable pain. Obesity is no contraindication to the procedure. Parietal cell vagotomy, likewise, in selective cases can be applied to the patient with an acute perforation and to some cases of massive hemorrhage where the surgeon is able to open the anterior duodenal wall distal to the pylorus and transfix the bleeding vessel without violating the integrity of the pyloric sphincter. Significant gastric outlet obstruction is a definite contraindication to the operation but in mild cases of obstruction where there is not appreciable retention, the pyloric outlet and duodenum may be safely dilated with a Maloney dilator and parietal cell vagotomy performed.[25] Johnston[29, 30] has recently stressed that in some cases of gastric outlet obstruction the stenosis may be located distal to the pylorus

and one may perform a *plasty* on the anterior duodenal wall distal to the pylorus to relieve the obstruction and then proceed with parietal cell vagotomy.

During the past 2½ years our group has been engaged in a prospective randomized study randomizing parietal cell vagotomy against truncal vagotomy-antrectomy and gastric selective vagotomy-pyloroplasty. Our work has not been reported to date but preliminary data parallel that of Johnston and others.[27, 28] In a group of approximately 100 patients we have experienced no mortality and the morbidity has been extremely low. No recurrent ulcer has yet appeared over the short follow-up study. Dumping symptoms have occurred in approximately 3 per cent of patients as compared to 20 to 25 per cent undergoing conventional operations for ulcer. Diarrhea has occurred in 1 per cent but has not been severe. With other operations for ulcer the incidence of diarrhea is around 10 per cent with approximately 1 per cent of patients experiencing disabling gastrointestinal symptoms. Secretory data on our patients are incomplete at present, but other groups have reported a reduction of BAO of 85 per cent which has remained constant up to 5 years. There has been some increase in PAO over the follow-up and this may be a cause for concern. Also a large number of patients undergoing parietal cell vagotomy are now experiencing a return in gastric acidity upon insulin stimulation, whereas during the early postoperative period the response to insulin was nil in over 95 per cent of the cases.

If one embarks upon the operation of parietal cell vagotomy it is mandatory that the operative technique be mastered from the beginning or else the operation is doomed to fail.[17, 35, 42] One should have a clear and precise knowledge of the anatomy of the neurovascular structures of the stomach and should not undertake the procedure unless first having been taught the fundamental steps by one's peers. Some of the early high recurrent ulcer rates following parietal cell vagotomy were no doubt due to inexperience with the technique, since subsequent reports by the same authors after gaining further experience shows a marked diminution in the ulcer recurrence rate. For the present, at least, I firmly believe that parietal cell vagotomy is still in the experimental stage and that it should be undertaken only by those individuals in university centers where patients can be thoroughly and adequately studied or by individuals with a thorough knowledge of the procedure who are engaged in prospective randomized studies.

It is my current feeling that vagotomy-antrectomy, preferably with a Billroth I reconstruction, is the most effective operation in current use to control recurrent ulceration. In those cases where the duodenum lends itself to resection, and this usually comprises 95 per cent of patients, it is our operative procedure of choice. Gastric selective vagotomy-pyloroplasty may in the future prove to be as effective as truncal vagotomy-antrectomy but additional long-term follow-up is necessary to adequately evalutate this operation. Truncal vagotomy-pyloroplasty, in my judgment, is not an ideal operation to use for the complications of ulcer. I feel its use should be restricted to the high-risk patient who undergoes either an elective or emergency operation in which the immediate salvage of life is of main concern and where consideration of long-

term protection against recurrent ulcer is not the main problem. If this philosophy is adhered to and if the high risk patients are omitted, vagotomy-antrectomy can be performed with as low an operative mortality as the lesser procedures and with a much better guarantee against future ulcer disease.

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Personal Observations and Experiences in the Diagnosis and Management of Ulcer Disease and Disabilities That Follow Peptic Ulcer Operations

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Most operations involving the stomach, particularly those for ulcer or cancer, may lead to unpleasant side effects. Those which lead to no side effects are operations which produce no physiologic change, e.g., gastrotomy, simple excision of a peptic ulcer, or the Ramstedt pyloromyotomy.

To be effective, any operation for chronic peptic ulcer must profoundly change the gastric physiology by bypassing or damaging the normal pyloric control of gastric emptying, by altering the acid, pepsin, and mucus secretion of the stomach, or by interfering with the antral hormone gastrin. As a result, the postprandial content of the upper small bowel is altered by its erratic entry, its bulk, and its stage of digestion. If the celiac branches of the vagus nerve are divided as in truncal vagotomy or in mass ligation of the left gastric artery in partial gastrectomy, then the innervation of the small bowel is also grossly disturbed and may further cause motility or digestive abnormalities. My own experience with duodenal ulcer surgery spans several decades when different operations were popular.

PYLOROPLASTY

One of the earlier operations used for duodenal ulcer was pyloroplasty (without vagotomy). Dumping symptoms are caused by the loss of pyloric control of gastric emptying. They were first described in association with gastrojejunostomy but may occur after any form of pyloroplasty. I first used pyloroplasty in the 1930's, usually a simple Heineke-Mikulicz procedure or the Judd modification in which an anterior duodenal ulcer was excised as well, but the physiologic disturbance was the same. I found too that a few patients complained of eructation of

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bile or gastric juice or vasomotor symptoms of flushing and palpitations, or faintness and fatigue. This was due to the loss of pyloric control of gastric emptying and I sought other alternatives to avoid these side effects.

GASTROJEJUNOSTOMY

Attempts were made to modify the standard gastrojejunostomy operation then employed for mild ulcer cases. These were patients with a low acid output, or who were frail. From 1940 to 1944, I modified the then standard technique by placing the stoma in the alkali-secreting pyloric antrum on the anterior wall with the efferent loop near the greater curve. I hoped to give gravitational drainage in this position, instead of placing it on the posterior wall in the most dependent part of the acid-secreting part of the stomach where the jejunum is constantly bathed in gastric juice.[17] This was done before data on gastric emptying were available. The role of gravity drainage today is of less importance than previously thought.

A decade later Swynnerton showed that the orthodox posterior gastrojejunostomy had a 50 per cent recurrent ulcer rate and the anterior juxtapyloric operation 26 per cent. These cases which did *not* ulcerate were about the best results he had seen after peptic ulcer operations and many patients with only minor degrees or isolated incidents of reulceration were highly satisfied. These operations have largely been abandoned today except in unusual circumstances.

Gastrojejunostomy was gradually replaced by partial gastrectomy for duodenal and gastric ulcer. The presumed benefit of this was the removal of hormonal stimuli (gastrin) as well as the removal of part of the acid- and pepsin-secreting body portions of the stomach.

PARTIAL GASTRECTOMY

The Billroth I (Pean) operation appeared to be physiologic and satisfactory in the treatment of gastric ulcer with a small, 2 to 4 per cent recurrent gastric or stomal ulceration rate. It proved unsatisfactory for duodenal ulcer because of a high recurrent ulcer rate. I now use it for duodenal ulcer only in association with vagotomy. The most popular operation for duodenal ulcer became some form of distal partial gastrectomy followed by a gastrojejunal reconstruction. This produced more side effects than gastrojejunostomy but the recurrent ulcer rate was low. A (minimum) 5-year follow-up (on two occasions) showed a 2 and 3 per cent rate of recurrent ulcers (many of which were not severe enough to require further operatión). The mortality was higher, however, but the author was able to report 120 gastrectomies with one death in 1943,[12] and since then our mortality for gastrectomy for duodenal ulcer has fallen to about 0.5 per cent. This relatively low figure is because better selection has avoided duodenal stump leakage.

After partial gastrectomy the incidence of dumping was very similar between the Billroth I and the Billroth II operations as shown by a follow-up of patients operated on between 1946 and 1949.[14]

A few patients noticed intestinal upset after this operation. Iron deficiencies may occur depending on food intake. A small number of patients have regurgitation of gastric or bilious reflux but this is troublesome in under less than 1 per cent and less than one in 200 requires a further operation for its correction.

Compared with truncal vagotomy, we found partial gastrectomy the more satisfactory operation,[16] and this was confirmed by Goligher et al.[7]

VAGOTOMY

Because of the imperfections of the partial gastrectomy operation (weight loss, reflux and dumping), Dragstedt reintroduced vagotomy in 1945.[4] I began a series of truncal vagotomies in January 1948. During the next 18 months, of 87 cases the routine was to perform simple truncal vagotomy in most cases where duodenal narrowing was minimal, and to add pyloroplasty where there was more severe narrowing. At the end of this period a follow-up showed that patients with the *worst* ulcers, i.e., those having pyloroplasty, had done well, but of 55 truncal vagotomies without drainage, 54.7 per cent (29 cases) were unsatisfactory. In most cases, the dissatisfaction was due to delayed gastric evacuation, causing offensive belching and postprandial discomfort.[14, 20]

The answer to the problem of retention after simple truncal vagotomy was solved by the addition of a drainage procedure at the primary operation. Of the 55 simple vagotomies done with drainage, results were satisfactory, without gross retention or ulcer recurrence, in 95 per cent.

The next task was to determine the best drainage operation to combine with truncal vagotomy. I compared the Heineke-Mikulicz pyloroplasty and gastrojejunostomy.

In a 5- to 10-year follow-up of 319 cases, 11 had recurrent ulcer (3.3 per cent). There was an interesting difference insofar as after vagotomy and gastrojejunostomy all recurrent ulcers were jejunal, whereas after vagotomy and pyloroplasty more than half the recurrent ulcers were gastric, the rest were duodenal.

Comparing truncal vagotomy and pyloroplasty with truncal vagotomy and gastrojejunostomy 5 years after surgery, the side effects were similar (Table 1).

Dumping has diminished with time. In many cases the symptoms were minor.

UNTOWARD SYMPTOMS THAT FOLLOW PEPTIC ULCER OPERATIONS

Before treating postoperative disabilities, it is first essential to diagnose their disorders. An accurate history must be taken. For example

Table 1. *Residual Symptoms 5 Years After Vagotomy and Drainage (319 Cases)*

	PYLOROPLASTY (202 cases)	ANTERIOR JUXTAPYLORIC GASTROJEJUNOSTOMY (117 cases)
Diarrhea	48 (24 per cent)	34 (29 per cent)
Hypoglycemia	61 (30 per cent)	32 (27 per cent)
Pain		
Ulcer-like	6 (3 per cent)	3 (2.5 per cent)
Non-ulcer cramps etc.	34 (17 per cent)	17 (15 per cent)
"Fullness"	101 (50 per cent)	57 (49 per cent)
Vomiting	8 (4 per cent)	2 (2 per cent)
Regurgitation	12 (6 per cent)	17 (14 per cent)
Dumping	4	2
Food intolerance	10 (5 per cent)	6 (4.5 per cent)

dumping is rare while the patient is recumbent and confined in the hospital, but it is common to have transient or more troublesome symptoms in the early weeks after leaving the hospital. In most cases the symptoms gradually abate, presumably as a result of the body's adaptation to the altered physiology. Thus, reoperation should not be done for most disorders under 1 year, during which time dietetic and medical management will be required.

Because some of these disabilities vary in severity it is tempting to regard the more obstinate ones (disabilities and patients) as being neurotic rather than organic. Nevertheless, the fact that patients having the same operation develop similar side effects which are unusual in the unoperated population points strongly to some of these sequelae having an organic background. It is true that during an emotional crisis postoperative disabilities may be more pronounced, and the neurotic or introspective patient will complain more, but this applies to many organic conditions, including peptic ulceration itself.

I believe it is therefore rarely of much help to send the patient with postoperative disabilities to the psychiatrist.

Dumping Syndrome

This is due to disruption or bypass of the pyloric sphincter mechanism and is seen with or without a gastric resection. I have observed it after all operations for duodenal ulcer that have included a drainage procedure or resection.

These symptoms include both vasomotor (flushing, sweating, tachycardia) and intestinal (cramps, diarrhea). The presentation may vary. Rarely, fatigue or fainting attacks after a meal may occur and those are in part due to the hyperosmolarity of jejunal contents resulting in loss of plasma volume into the bowel lumen.[1, 11] Such symptoms may be accompanied by borborygmi and postprandial diarrhea. Because of the great fluctuation in blood glucose levels some patients may faint or even have

hypoglycemic fits. The diagnosis in such cases depends on the astute physician taking blood for glucose determinations during such attacks.

This condition may be illustrated by the case of a sexagenarian patient who had an excellent overall result following partial gastrectomy for duodenal ulcer. He lived in the country but had a small apartment in London. On two occasions, each while he was in London, he had collapsed about 2 hours after breakfast and was admitted to a hospital where he rapidly recovered after glucose was administered. On questioning him we found that in the country his breakfast was bacon and eggs. In town he would have cereal with sugar, milk, and coffee. No doubt the rapid entry of the latter high fluid and carbohydrate diet was the cause of the fluctation in his blood sugar. Explanation of the cause and a change in his town breakfasts solved his problem.

Assays of the kinin levels in dumping patients with vasomotor symptoms show that the kinin levels are elevated.[23] A return of kinin levels to normal follows a successful operation for dumping symptoms (jejunal interposition). In those in whom symptomatic relief does not occur following surgery the kinin levels remain elevated.[3] This certainly points to an organic cause for at least one of the more common postoperative disabilities.

Before undertaking an operation for dumping my experience has shown that iron deficiency anemia or a low blood volume should be corrected.[18]

An Arab patient was quite incapacitated after meals by vasomotor symptoms and faintness. He had had a vagotomy with gastrojejunostomy some years before for duodenal ulcer, and in 1960 I recommended dismantling of the gastrojejunal anastomosis and the performance, if necessary, of a short pyloroplasty. Before the operation it was discovered that the patient had a low hemoglobin and after closer questioning that he was losing blood daily from hemorrhoids. The operation was therefore changed to simple hemorrhoidectomy which terminated the blood loss, and a few weeks later the patient was able to give a 6-hour speech to his country, and the problem of troublesome dumping never occurred again!

Another indication of the importance of iron deficiency was shown in Wastell's[55] 11 to 20-year follow-up of 192 of the author's cases of truncal vagotomy with drainage. Ninety-seven per cent of the patients with vagotomy and pyloroplasty were satisfactory, but after vagotomy and gastrojejunostomy 91.2 per cent were satisfactory. The difference was that the latter series had lower serum iron and hemoglobin values, perhaps contributing to subclinical anemia and dumping. By giving iron orally to the latter group the percentage of satisfactory cases rose. There are many advantages in the truncal vagotomy and gastrojejunostomy, but it is important to advise these patients to have regular blood examinations, or perhaps to take oral iron regularly.

If these deficiencies are corrected and dietary management has failed to control dumping, an operation may be necessary.

The operation I have most commonly used for this was suggested by Henley in 1952[8] and consists of interposing a reversed limb of jejunum

between stomach and intestine. It is done as a secondary procedure. It is not used as a primary operation because of the high risk of recurrent ulceration. An interposition of a reversed loop of jejunum greatly delays gastric emptying. I first used this on a postgastrectomy patient thought to have an epileptic seizure. He was hypoglycemic and was referred by a neurologist. The gastrectomy was dismantled, continuity was established by connecting the stomach remnant with the duodenum, and a reversed jejunal loop of 4 cm was placed between the gastric stoma and duodenum. Thereafter the patient had no more 'fits' and no more dumping.

With regard to the interposition of an antiperistaltic loop of jejunum, it must be remembered that there is a critical length, above which troublesome gastric retention may occur (Fig. 1). This critical length depends on whether a vagotomy has been carried out. Generally speaking 3 to 4 cm of unstretched reversed jejunum between the gastric stoma and duodenum is adequate to prevent rapid emptying of the stomach, though this may mean utilization of 10 to 14 cm of jejunum. If gastric emptying is delayed enough to cure dumping, then any weakness of reflux in the gastroesophageal sphincter mechanism may be evident and worsened. On more than one occasion repair of a hiatus hernia with reflux was necessary after an interposed jejunal limb. Dumping symptoms that follow vagotomy with pyloroplasty or gastrojejunostomy with antrectomy may be treated by the reversed jejunal limb. Dumping following vagotomy and pyloroplasty may be dealt with by an operation called pylororrhaphy or pyloric reconstruction. This was first done by me in January 1970. Quite independently Christiansen, Hansen, and Pedersen[2] used an almost identical procedure in 1972 and reported five satisfactory cases in 1974. This entails exposure of the pyloroplasty and incision and opening of the suture line (Fig. 2). The divided ends of the pyloric sphincter are identified. A No. 32 nasogastric tube is passed and the severed ends of the pylorus are united with catgut suture over the nasogastric tube. The incision is then repaired longitudinally, restoring the pyloric musculature. If it proves impossible to close the incision over the tube, as a result of ulcer fibrosis, a shorter pyloroplasty or duodenoplasty will be required. After the operation the nasogastric tube is replaced by a smaller nasogastric tube placed beyond the pylorus, and the patient is fed through this until oral feedings are started.

There may be a delay in gastric emptying for 1 to 3 weeks after this operation. The only permanent delay occurred in a case where it proved difficult to close the pylorus adequately over the gastric tube and later gastric drainage was required.

After successful repair cases near normal anatomy is seen on radiographic examination (Fig. 3).

Bilious Vomiting

This rare problem may occur after gastrojejunal anastomosis, pyloroplasty, or the Billroth I operation, though it is usually less severe in the latter procedures. It is covered in detail elsewhere in this volume. The patient typically complains of epigastric burning which is relieved by

Figure 1. Interposed antiperistaltic reversed jejunal limb for treatment of dumping syndrome.

vomiting bile. As much as a liter of bile may be brought up in a day. Anorexia, wasting, and in longstanding cases, pulmonary tuberculosis, mental depression, or suicide may follow. In severe cases medical management offers little and an operation, usually some form of Roux-en-Y conversion, will be needed. Before operation one must be certain that the vomited fluid is bile. The reason for this is that many patients may regurgitate a little juice and because it tastes bitter, call it bile. A Roux conversion will do little to improve vomiting of gastric juice and wellnigh all the failures after Roux conversion are due to a wrong preoperative diagnosis of inflammatory changes in the stomach.

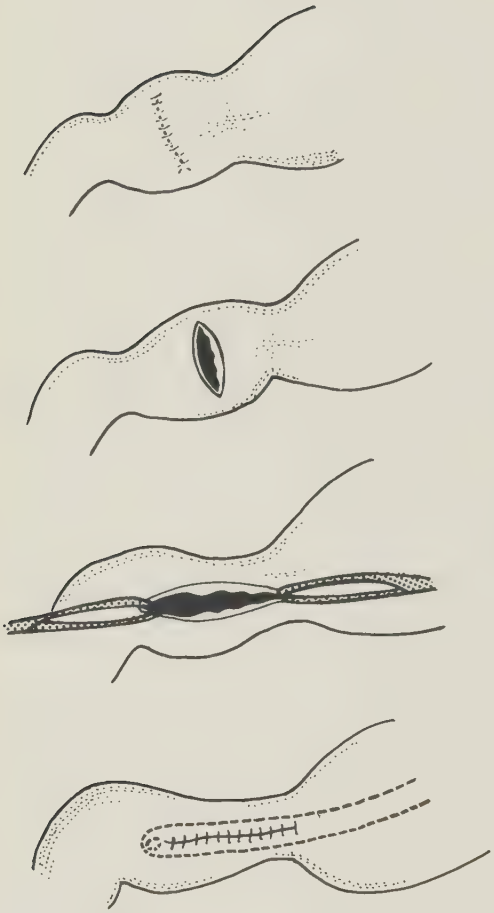

Figure 2. Pylororrhaphy. Pyloroplasty incision is opened transversely and closed longitudinally over a 32 French nasogastric tube.

Figure 3. An opaque meal after pylororrhaphy. The pylorus looks normal.

In the past, bilious vomiting has been thought to be due to the intermittent release of bile in the afferent loop, and it has been called the "afferent loop syndrome." In my opinion there is no such condition and the real cause of the burning pain is bilious gastritis, hence its relief by vomiting bile.[19]

With regard to conversion to a Roux anastomosis, this may be difficult and time-consuming, particularly if the gastrojejunal anastomosis is retrocolic, or if there are dense adhesions in the abdomen.

Therefore, in conversion to Roux anastomosis the author introduced the "Roux 19" conversion in 1950 (Fig. 4). In this modification, the transverse colon is found and the inferior surface inspected. The afferent jejunal loop is at once found. The efferent loop is next identified. The afferent loop is transected and each end held in a fine crushing clamp. The distal (gastric) end is anastomosed end-to-side to the highest convenient part of the proximal efferent loop. The proximal (duodenal) end, carrying

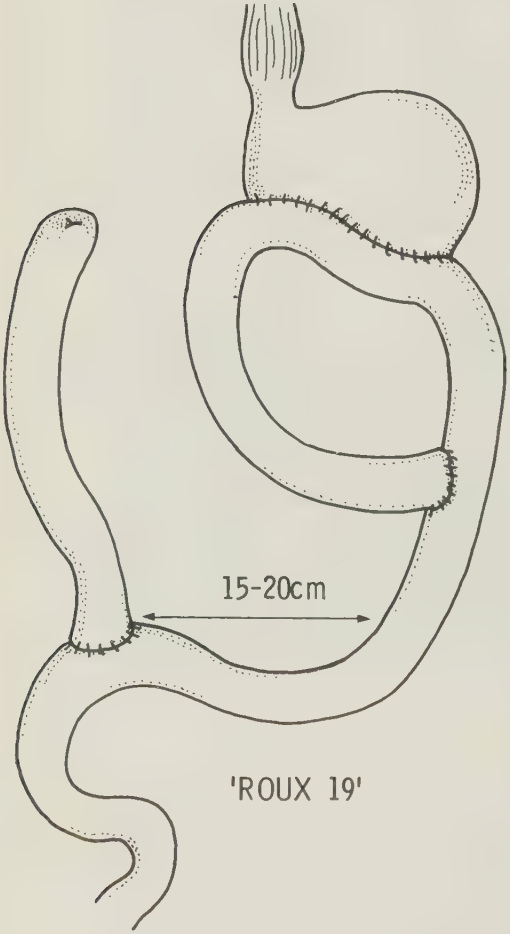

Figure 4. A Roux "19" conversion.

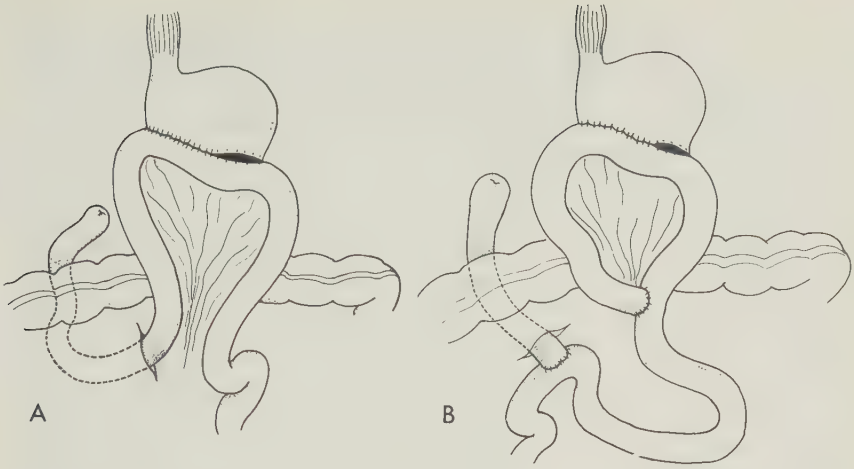

Figure 5. *A*, An antecolic valved partial gastrectomy, associated with bile vomiting. The afferent loop is usually of normal calibre. *B*, The same after Roux "19" conversion.

the bile and duodenal and pancreatic secretions is anastomosed end-to-side to the efferent loop 15 to 20 cm beyond the first anastomosis. This will carry the biliary secretions well away from the stomach and eliminate any possibility of bilious gastritis or vomiting (Fig. 5). An additional advantage of the "Roux 19" is that both efferent and afferent exits from the stomach remain, improving gastric emptying, bearing in mind that some cases of bilious vomiting or gastric distention are due to efferent loop kinking or obstruction.

Diarrhea

This is covered in detail elsewhere in this volume. After partial gastrectomy, I have noted that in some patients without vagotomy there is a tendency to colonization of the small bowel with colonic bacteria. If this is the cause of diarrhea, treatment for 5 to 6 days, two or three times a year, with a sulfonamide intestinal antiseptic may be helpful. If the diarrhea is episodic with severe bouts lasting a day or two, then it is possibly due to inadvertent vagotomy, for a ligature around the main pedicle of the left gastric artery will, unless great care is taken, also encircle and damage the celiac branch of the posterior gastric nerve. Certainly the best means of treating this diarrhea is prevention. Selective and highly selective vagotomy have been suggested as ways of decreasing the incidence of diarrhea after vagotomy.

In 1948 Jackson[9] suggested that only the stomach needed denervating, and that the pancreatic and celiac branches of the vagus nerves could be spared. Various methods of effecting this have been described.[20]

Selective vagotomy appeared to abolish the problem of severe diarrhea. The operation was still far short of perfection in a small number of

cases because of the loss of pyloric control, due to the associated drainage procedure. Thus, in common with many other surgeons, in 1970 I commenced to use the highly selective (proximal gastric) vagotomy, cutting all the nerves to the body of the stomach, but preserving the nerve of Latarjet to the antrum. It was suggested that in cases of duodenal stenosis a pyloroplasty should be added. This seemed to nullify the purpose objective of the highly selective operation, which was to abolish dumping and diarrhea. Thus, in November 1970 I introduced duodenoplasty,[5] which briefly consists of making a longitudinal incision over the narrow part of the duodenum, followed by transverse resuture after the fashion of Heineke-Mikulicz pyloroplasty, but avoiding incision into the pyloric sphincter (Fig. 6*A*). In cases with a stenosing superior duodenal and a large inferior diverticulum a Finney type of procedure may give better drainage, again avoiding damage to the pyloric ring (first used in April 1971) (Fig. 6*B*). The operation of highly selective vagotomy with duodenoplasty in a minority of cases has since been extensively practised by my successor at St. James's. He has found it effective even in gross stenosis with retention. Since November 1970 at St. James's Hospital, London, the highly selective operation has been employed in 278 cases, 32 required a duodenoplasty. Despite the newer vagotomies, there are many truncal vagotomies still carried out, and bearing in mind the satisfactory 11 to 20 year result in our own cases, one cannot campaign against truncal vagotomy. Greater expertise is

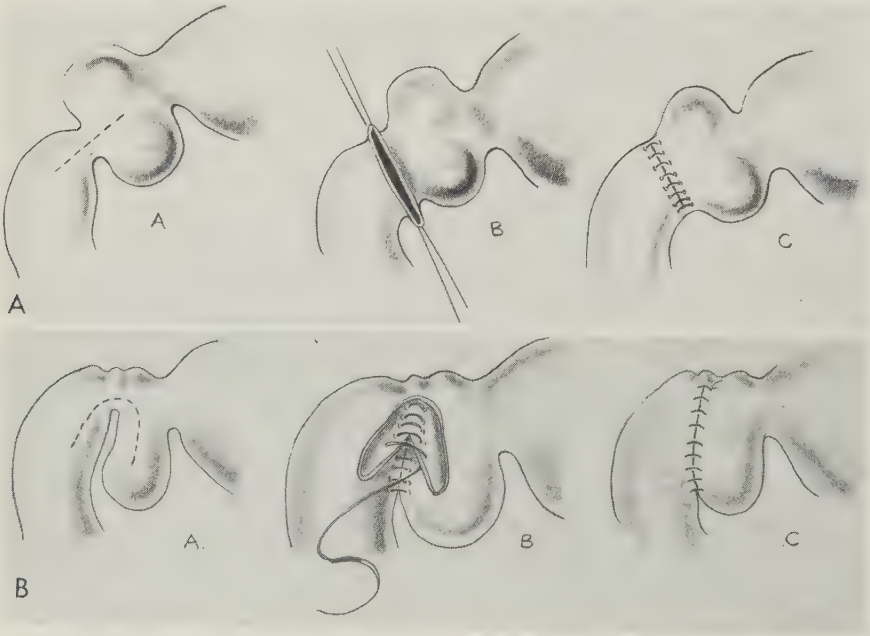

Figure 6. *A*, Duodenoplasty similar in design to a Heineke-Mikulicz pyloroplasty. *B*, Duodenoplasty similar in design to a Finney pyloroplasty.

Figure 7. A reversed loop seen at laparotomy over a year after surgery. The suture lines are indicated. The proximal bowel is dilated while the distal segment is normal in calibre. *B*, An opaque meal shows dilatation of the small bowel following reversal of 14 cm of ileum.

required for the selective procedures, and the safety of truncal vagotomy has been impressive.

However, of many hundreds of truncal vagotomies personally carried out and cases sent from other clinics, five cases of diarrhea were severe enough to warrant surgical reintervention. The only procedure found to be of help was a reversed small intestinal loop.[6] Arbitrarily it was decided to reverse 14 cm of ileum, and place it two-thirds of the measured distance between duodenum to the ileocecal valve.

This was effective in five cases of diarrhea. Tried in a sixth case for dumping it failed. In two cases it was possible to examine the reversed loop a year or more later.

In each case a variable degree of colic followed the operation. The reversed loop had acted as a subacute small bowel obstruction, with dilatation before the loop (Fig. 7). A barium roentgenogram showed the dilatation above the reversed loop (Fig. 7*B*). This operation, used for 9 years, remains our main surgical solution until a better answer is found.

Conversion Operation

For many years I changed a gastrojejunal anastomosis by converting it to a gastroduodenotomy (Billroth I). This was done before Roux-en-Y anastomosis or interposed jejunal segments were popular. My results at 5 or more years are shown in Table 2. They are compared to a

Table 2. *Results 5 Years or More After Billroth I Conversion Operations (Gastroduodenal Anastomosis)*

SYMPTOM	NO. OF CASES	CURED	IMPROVED	UNCHANGED	WORSE
Total	55	14	37	3	1
Bilious vomiting	34	11	12	10	1
Fullness, pain or nausea p.c.	29	13	12	4	0
Vasomotor	14	4	6	4	0
Diarrhea	10	0	7	1	2

subsequent group who had a Roux 19 conversion (Table 3). The superiority of "Roux 19," although the Billroth I occasionally cures bilious vomiting, is evident and the "unchanged" group for bilious vomiting after "Roux 19" are, I am sure, cases of inaccurate diagnosis.

A most interesting feature of the conversion to Billroth I was that between one-third and one-half of those unable to take milk or eggs before operation tolerated them with comfort after surgery. The same applied to the "Roux 19," after which two-thirds of those unable to take milk and eggs were able to do so. I am uncertain of the mechanism involved. Since the "Roux 19" is simpler it is now much more frequently used than Billroth I conversion today.

Recurrent Ulceration

Many of these modifications may increase gastric secretion by reducing gastritis and thereby increase the risk of recurrent ulceration, particularly if a vagotomy has not been carried out. One should listen carefully to any complaints the patient may make which indicate the possibility of recurrent ulcer disease after any of these operations.

Table 3. *Results 5 Years or More After "Roux 19" Conversion Operations*

SYMPTOM	NO. OF CASES	CURED	IMPROVED	UNCHANGED	WORSE
Total	41	23	10	4	4
Bilious Vomiting	29	23	4	2	–
Fullness, pain or nausea p.c.	18	9	6	2	1
Vasomotor	5	1	1	3	–
Diarrhea	3	–	2	1	–

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Selective Visceral Angiography in the Diagnosis and Treatment of Gastroduodenal Hemorrhage

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The role of the radiologist in the evaluation of the patient with symptoms of a peptic ulcer has, in some respects, changed very little. The radiologist remains primarily a morphologist as he goes about every Spring and Fall filling ulcer niches with barium sulfate and searching for ulcer mounds, radiating folds, Hampton's lines, and, occasionally, free intraperitoneal air. The diagnostic criteria for distinguishing between benign ulcers and malignancy have been established. Vast numbers of peptic ulcers are visualized, diagnosed, and followed successfully by roentgenographic techniques.

A significant number of ulcer patients require hospitalization because of recurrent symptoms or development of complications. It has been estimated that about 25 per cent of ulcer patients require hospitalization for hemorrhage.[23] Acute hemorrhage may often be the first symptom of an ulcer, and may develop without warning. In these instances efforts to localize the site of bleeding, determine the etiology, and then treat are necessary. Advances in angiography and pharmacoangiography have enabled the radiologist to complement his colleagues, particularly the endoscopist and the surgeon. His role today is both diagnostician and therapist.

Within a generation, gastrointestinal angiography has grown from an academic curiosity to a very useful diagnostic and therapeutic tool.[22] Rostelli[22] first demonstrated gastrointestinal bleeding by angiography in 1959 when he showed extravasation of contrast material into the duodenum of a patient who had died from a bleeding ulcer. In 1960 Margulis et al.,[10] using intraoperative arteriography, demonstrated acute gastrointestinal bleeding from both a bleeding colonic neoplasm and an intestinal arteriovenous malformation. In 1963, Nusbaum and Baum[12] clinically used selective angiography and demonstrated that as little as 0.5 cc of bleeding per minute could be identified. These lesions were produced in animals. The minimal rate of bleeding that can be detected in humans is unknown; estimates range from 0.5 to 3 cc per minute.

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Since then numerous articles have appeared establishing the usefulness of angiography in the localization of hemorrhage throughout the gastrointestinal tract.

Again, Nusbaum et al.[15] in 1967 introduced selective pharmacoangiography for the control of bleeding esophageal varices. Although the use of systemic vasoconstrictors had been suggested for the control of hemoptysis as early as 1911,[29] and intravenous administration for control of variceal bleeding in 1956,[9] Nusbaum et al. showed that portal hypertension and variceal bleeding could be controlled by selective infusion of Pitressin into the superior mesenteric artery.[13] Subsequently, in another group of patients, they were able to control arterial gastrointestinal hemorrhage as well.[2, 14] Since the late 1960's angiographic technique has progressed and, in addition to infusion of vasoconstrictors,[21, 25] autologous clot,[19, 27] Gelfoam,[26] polyvinyl alcohol, modified Foley balloon catheters,[28] Silastic and epoxy glues[6] have at one time or another been used to occlude or sclerose bleeding vessels. More importantly, these techniques are routine in residency programs, and are now available throughout the country.

INDICATIONS IN BLEEDING ULCERS

Emergency angiography is indicated for acute hemorrhage when the site of hemorrhage is unknown (when vital signs are maintained by replacement). The history and physical findings are clues to where the hemorrhage may originate. In a significant number of patients (perhaps 50 per cent) with previously diagnosed esophageal varices[11] and peptic ulcers, the site of hemorrhage is from other lesions. Bright red blood passed by rectum usually indicates lower gastrointestinal bleeding, but may in fact result from brisk duodenal hemorrhage. The results of exploratory surgery, when the source is not established preoperatively, have not infrequently resulted in uncomfortable and frustrating moments for surgeons. Therefore, vigorous attempts to localize accurately the bleeding site by endoscopy or angiography or both are warranted before surgery, even in acute bleeding.

The use of endoscopy has increased as instruments have improved. Bleeding from the upper gastrointestinal tract can be visualized from the esophagus to the ligament of Trietz, and endoscopy often obviates the need for further diagnostic investigation. There are some limitations to endoscopy, however. In patients with varices the distinction between portal venous and arterial bleeding is sometimes difficult, and a significant number of patients diagnosed to have bleeding varices are subsequently found by angiography to have arterial bleeding. Likewise, in a patient with profuse hemorrhage, copious amounts of fresh blood and clot may obscure the site of origin. Lastly, little can be done at endoscopy to control bleeding.

Angiography may not only accurately localize hemorrhage, but in patients who are at high risk from immediate surgery because of compromised renal, cardiac, or pulmonary functions, bleeding may be at least temporarily controlled by selective infusion of vasoconstricting

drugs. This significantly reduces blood loss[5] and allows better preparation of an emergency patient. Because bleeding in ulcer disease may occur in self-limited episodes, if angiography is contemplated, it should be done while the patient is actively bleeding.

The use of barium is mentioned only to be deprecated. Barium studies should not be initially done in acute bleeding and are indicated for patients with chronic blood loss or after bleeding has been controlled, but the source not localized. Barium in acute bleeding obscures physical and roentgenographic landmarks and precludes visualization of the bleeding site by angiography for at least 24 hours. Whether angiography should precede endoscopy is academic. These procedures complement each other and their use will depend on local situations at every hospital.

TECHNIQUE

The patient should be accompanied to the angiographic suite by the physician responsible for the patient. Percutaneous catheterization via the femoral or axillary approach by the Seldinger technique is followed

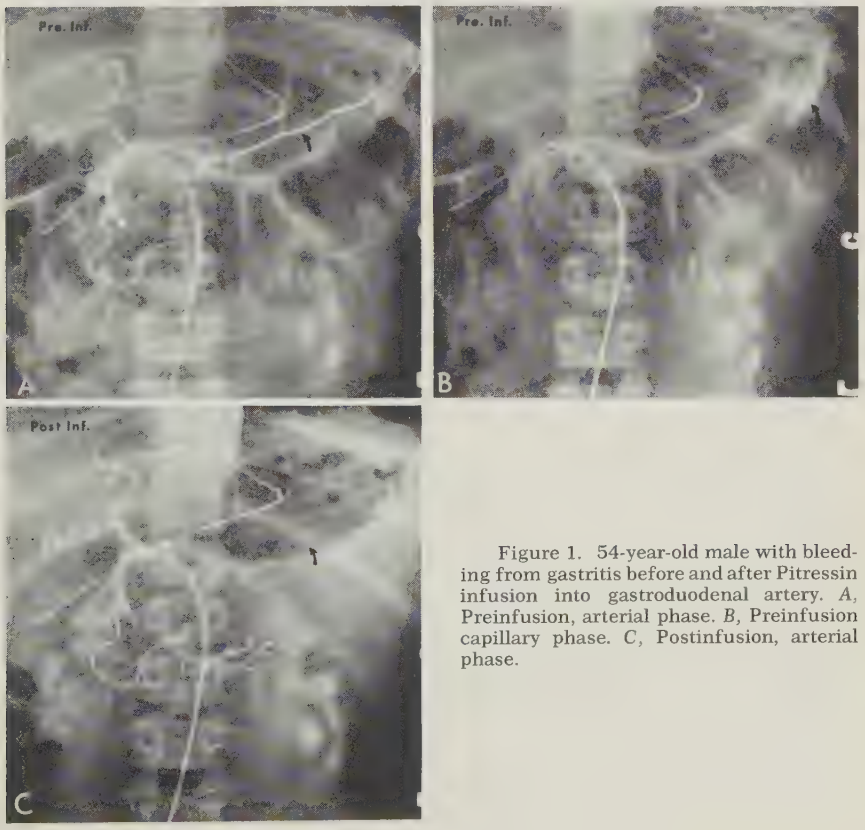

Figure 1. 54-year-old male with bleeding from gastritis before and after Pitressin infusion into gastroduodenal artery. *A*, Preinfusion, arterial phase. *B*, Preinfusion capillary phase. *C*, Postinfusion, arterial phase.

by selective injection of iodinated water soluble contrast material into the celiac, superior mesenteric, or inferior mesenteric arteries. The order of injection is indicated by historical and endoscopic findings. Magnification and subtraction techniques, when available, may help in localizing a small bleed, but are dependent on the patient's cooperation, and are seldom necessary in acute bleeding. Once the site of hemorrhage is identified, the vessel nearest the site is selectively catheterized. Pitressin is infused at a rate of 0.2 units per minute for 15 minutes, and the angiogram is repeated using the same technique and rate of injection. The rate of infusion is then titrated as needed to control hemorrhage or until a limiting dose rate of 0.4 units per minute is reached.

Immediate surgery is necessary when bleeding is not controlled by Pitressin. If the patient is a poor surgical risk, and if the catheter is subselectively placed near the bleeding site, autologous clot, Gelfoam mixed with clot, or a Fogarty catheter can be used to occlude the bleeding vessel. Autologous clot may recanalize after several days, whereas Gelfoam forms a permanent occlusive plug.

If bleeding ceases with the Pitressin infusion, a sterile dressing is applied over the entry site of the catheter and the patient is transferred to an intensive care unit. A combination wall current/battery operated pump permits continuous delivery at a controlled rate. Following the procedure, the urinary output should be monitored, and the site of the arteriotomy and peripheral pulses routinely inspected. If no further bleeding occurs, the rate of infusion is halved at 24 hours, dextrose and water is begun at 48 hours, and the catheter is removed at 72 hours.

COMPLICATIONS

The reported complications from angiographic infusion of Pitressin are many and varied. The reported incidence of complications varies from less than 10 per cent to more than 35 per cent. The complications range from a simple dislodgment of the catheter from the selected artery to respiratory and cardiac collapse. They can, however, be dually categorized as those related to placement of the catheter and those secondary to infusion of Pitressin.

Catheter migration, clotting of the catheter, bleeding around the catheter and hematoma formation or thrombosis at the site of the arteriotomy, peripheral embolization, and septicemia are related to placement of the catheter and its maintenance for prolonged periods of time. Catheter migration is the most common cause of infusion failure and can be minimized by puncture high in the common femoral artery away from the bifurcation and by proper fixation in the groin. Bleeding around the catheter and hematoma formation are usually related to abnormal blood clotting, but are evident at the time of catheterization and can be treated by removal of the catheter and compression. Major complications secondary to thrombosis, embolism, and septicemia are much less common, but their incidence increases with prolonged catheterization and infusion. Aseptic conditions must be maintained at the arteriotomy site and pulses checked hourly. Meticulous care of the arteri-

otomy site will minimize complications, but when they occur the infusion must be terminated.

Pitressin is a purified extract of antidiuretic hormone which has been separated from the oxytoxic component. It acts directly on the muscularis producing vasoconstriction. Its effect is independent of innervation or sympathomimetic blockers, and the effect is reversible soon after infusion is discontinued. Systemic administration causes hypertension and constriction of the coronary arteries. Gastric motility is increased and water is retained. Tachyphylaxis also occurs. Most of these side-effects are minimized by local intra-arterial infusion since the

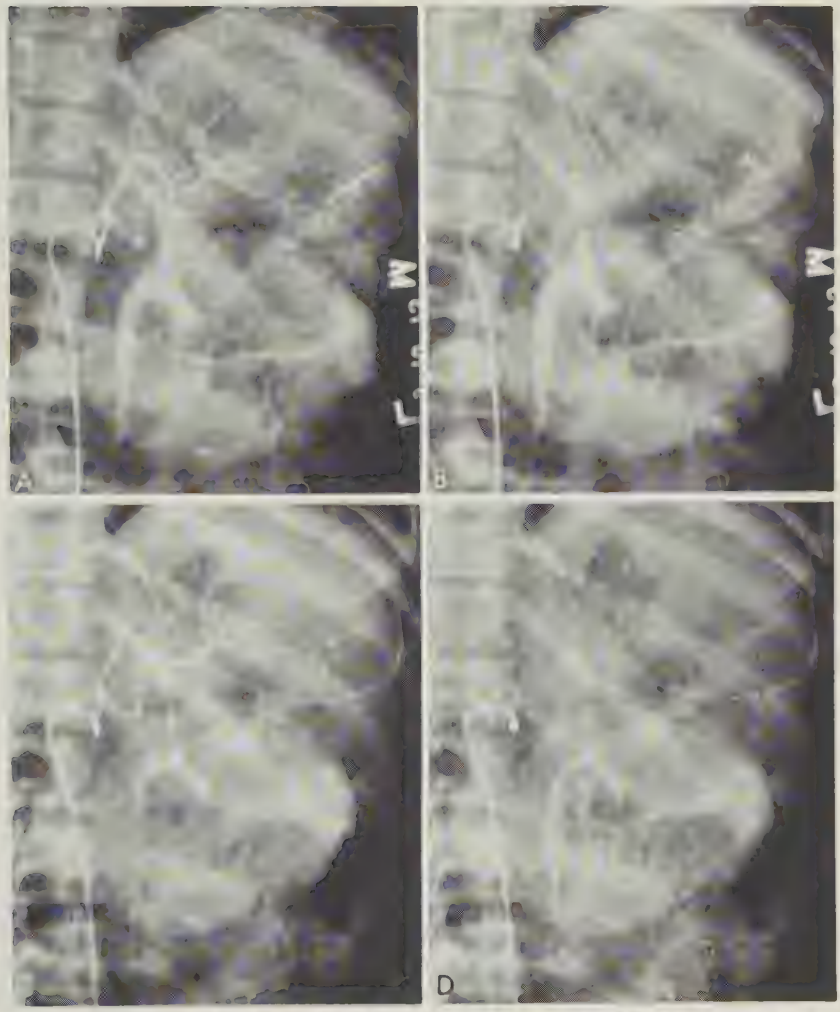

Figure 2. Selective left gastric angiogram on a 27-year old male with a tear of the gastric mucosa after a motorcycle accident. *A* and *B*, Pre-infusion study showing active bleeding in fundus of stomach on arterial and venous phase. *C* and *D*, Postinfusion study showing significant decrease in bleeding. Patient fully recovered.

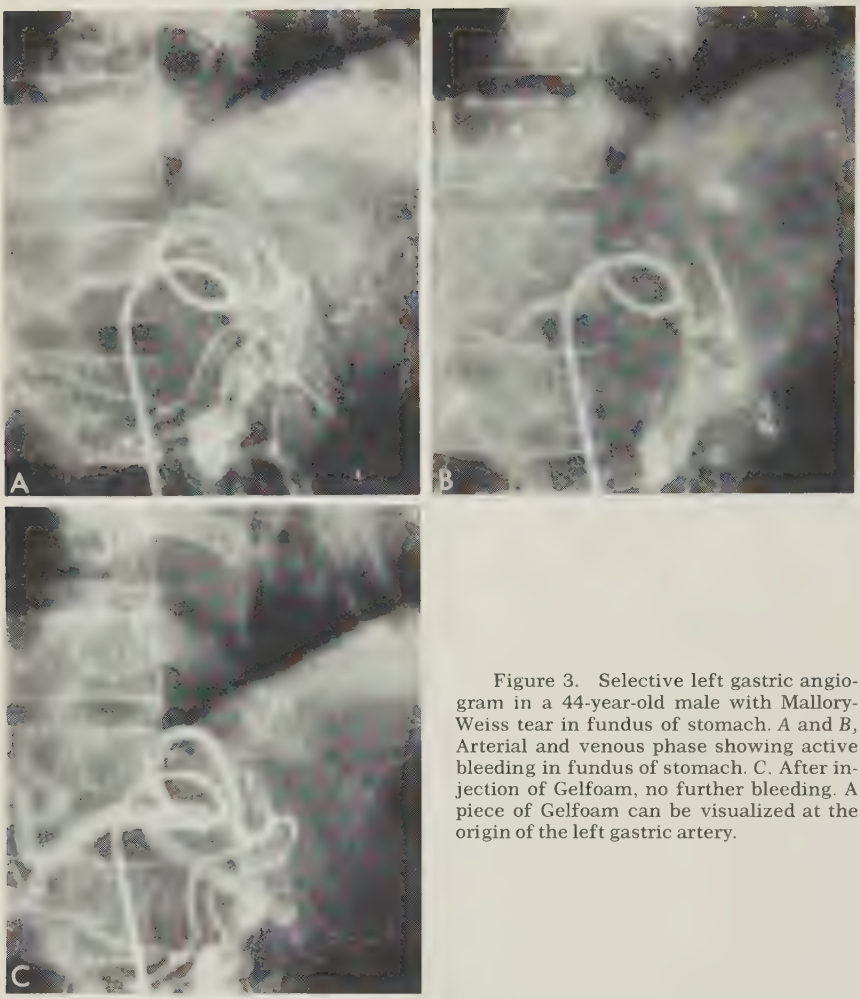

Figure 3. Selective left gastric angiogram in a 44-year-old male with Mallory-Weiss tear in fundus of stomach. *A* and *B*, Arterial and venous phase showing active bleeding in fundus of stomach. *C*. After injection of Gelfoam, no further bleeding. A piece of Gelfoam can be visualized at the origin of the left gastric artery.

liver is thought to detoxify the drug. Nevertheless, hypertension and a variety of cardiac arrhythmias ranging from bradycardia to ventricular tachycardia have been reported. Congestive heart failure secondary to water retention has occurred. Several cases of mesenteric vein thrombosis and bowel infarction have been reported as well, but these occurred in hypotensive patients who had infusions because of variceal bleeding.[3, 17] Earlier fears of hepatic necrosis with infusion of the celiac axis appear to be unfounded.[4, 7]

Our experience between 1972 and 1974 includes more than 200 examinations for hemorrhage. Eight-four patients have been evaluated for acute bleeding, and 23 infusions of Pitressin resulted in a low complication rate and no deaths. The complications consisted of three large hematomas (one of which required surgical intervention), one case of Pseudomonas septicemia, one case in which the gastroduodenal artery was dissected without sequelae, and one patient in whom bradycardia developed. Although five of these six complications occurred in patients who had been infused, more recent experience indicates a lower complication rate. With careful technique and close monitoring of vital signs, pulses, and urinary output the complication rate should be minimal.

COMMENTS

The value of angiography in identifying the sites of an acute gastrointestinal bleed has been established.[1, 8, 12, 14, 24] In a review of 250 patients in six published series,[1, 3, 8, 14, 16, 24] the site of acute hemorrhage was correctly identified in 156 (65 per cent). This compares with our experience in which the site of hemorrhage in 42 of 62 patients (68 per cent) with acute arterial hemorrhage was identified. The control of gastrointestinal hemorrhage with Pitressin has been established for Mallory-Weiss tears, gastritis, superficial and stress ulcer, as well as for control of lower intestinal bleeding, particularly from diverticula.[1-3, 5, 14, 18, 20, 21] The results for bleeding peptic ulcers, however, are less satisfactory for several reasons. Vasoconstrictors are most effective for small arterial and capillary bleeding, whereas duodenal ulcers that bleed often involve the gastroduodenal artery. In older patients this large artery may be involved by atherosclerotic changes. Also the dual blood supply to the gastric antrum and duodenum compensates for constriction of either the superior mesenteric artery or the celiac axis, providing continuous blood flow despite infusion. Subselective catheterization of the gastroduodenal artery may be difficult, and diffusion and dilution, for instance, by infusion of the celiac axis will decrease the drug's efficacy. Of the 23 patients in whom we infused, hemorrhage was successfully controlled in 14. Of the seven patients with bleeding peptic ulcers four were controlled and three were not. The gastroduodenal artery was selectively catheterized in the controlled patients, and either the celiac or superior mesenteric arteries were infused in those not controlled. These results plus our recent experiences emphasize the importance of selective catheterization. There is, however, no way to predict, and occasionally a large

duodenal vessel is controlled, at least temporarily, by infusion of the celiac axis. Use of preformed catheters has made subselective arterial catheterization easier to perform. In addition, simultaneous infusion of both the celiac axis and superior mesenteric artery has been used for control of duodenal bleeding, and when conventional techniques fail, Fogarty balloon catheters or injection of autologous clot may effectively stop arterial hemorrhage. While these clots may fragment and embolize distally causing segmental necrosis, this is an unusual complication. Nevertheless, when this technique is employed this complication must be kept in mind.

In summary, angiography enables the radiologist to complement the gastroenterologist and surgeon in the diagnosis and therapy of gastrointestinal hemorrhage. The combination of endoscopy and angiography makes it possible to quickly and accurately localize bleeding, to convert many emergency situations to elective procedures, and occasionally, to provide therapy via relatively noninvasive procedures. Definitive therapy remains surgical, but in those patients who are poor surgical risks, angiography offers an alternative form of treatment.

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Medical Management of Bleeding Duodenal Ulcers

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This review examines the nonsurgical methods presently utilized or proposed to treat bleeding from duodenal ulcers. The subject of intravascular delivery of drugs or other agents is dealt with elsewhere. Although treatment directed at the consequences of bleeding or at coexisting medical problems materially influences the outcome of the bleeding patient, these are not discussed. This discussion focuses on those modalities designed to influence the bleeding itself.

Nonsurgical management of bleeding from duodenal ulcer is the subject of many reports. Extracting firm judgments from this voluminous literature is, however, difficult. Some of the reasons for this difficulty include:

1. Upper gastrointestinal bleeding whether due to duodenal ulcer or other lesions tends to be self-limited. This appears to be true whether or not any particular therapy is used. Thus it is difficult to be sure whether any mode of treatment is of real benefit.
2. In many reports, all patients bleeding from the upper gastrointestinal tract are lumped together. Since the real concern consists of that subgroup with serious bleeding, "lumping" also makes judgments uncertain.
3. Controlled studies (placebo vs. the trial therapy) are not available and may not be feasible. Most physicians probably would not agree to withhold therapy from "control" patients even if the therapy has not been proven (at least in a statistical sense) to be beneficial. Experience, both personal and learned, plus the physician's need to intervene in such a serious situation, impels treatment. Controlled studies ("acceptable therapy" vs. "acceptable therapy") are similarly unavailable. Presumably the large individual variation in what is perceived as "acceptable," the difficulties in assembling well-matched groups, and the problems involved in applying an adequate protocol by an interested team in situations where the problem to be studied must be approached at all hours and at any time of the week or year, all play a role. Thus, all reports are essentially anecdotal.
4. Medical treatment is rarely confined to one approach alone. Under usual, clinical circumstances, how can one tell what worked? Was it bed rest, sedation, nasogastric suction, lavage, cooling, milk drip—or was this patient going to stop bleeding anyway?
5. Not all treatment modalities may be equally efficacious in treating each

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cause of upper gastrointestinal bleeding. For example, intragastric instillation of norepinephrine may be more effective in hemorrhagic gastritis than it is in duodenal ulcer bleeding. In most reports the cause of bleeding is not accurately defined. Although controversy exists[27, 35] as to whether emergency upper endoscopy leads to improved prognosis in the bleeding patient, it is clear that early endoscopy is the most accurate means presently available for precisely identifying the upper gastrointestinal bleeding site. Relatively few studies concerning therapy have used early endoscopy to define the location of bleeding. Endoscopy performed later in the course, roentgenographic studies or even subsequent surgery (unless performed while the patient is still actively bleeding) are less accurate.

The medical treatments for actively bleeding duodenal ulcers discussed include:

1. Feeding and continuous intragastric drip therapy
2. Intragastric lavage
3. Gastric cooling
4. Levarterenol instillation
5. Controlled gastric pH
6. Endoscopic control techniques
7. A group of miscellaneous therapeutic approaches

In the following sections these treatment methods will be analyzed and the accumulated experience summarized. Because of the previously mentioned limitations definitive conclusions can rarely be stated.

FEEDING AND CONTINUOUS INTRAGASTRIC DRIP THERAPY

Before Meulengracht, standard therapy for upper gastrointestinal bleeding consisted of bed rest, sedation (frequently with the use of morphine), and starvation. Bleeding was generally assumed to be due to peptic ulcer disease. This assumption certainly, by later studies, must have been highly inaccurate. It is of interest, however, that mortality figures ranged from 8 to 10 per cent. In 1947 Meulengracht[24] summarized 1031 cases treated with a frequent-feeding pureed diet. The patients were allowed to eat as much of the diet as they wanted. Water and milk were left by the bedside and patients were urged to drink these freely. All patients had "bleeding peptic ulcers." The exact diagnosis of the bleeding site was rarely established and blood transfusion used infrequently. Only 26 patients (2.5 per cent) died. This is an amazingly low figure, especially when one considers that these patients were treated without "benefit" of intensive care units, multiple transfusions, central venous pressure lines, emergency endoscopic or radiologic investigations, medical-surgical teams, and all the other assorted personnel and paraphernalia surrounding today's bleeding patient. One would be hard-pressed to find a modern, unselected series of patients with peptic ulcer bleeding with a mortality rate as low as Meulengracht's series. Patients in Meulengracht's series all had hematemesis or melena. Patients with small quantities of blood in the vomitus or with melena only detected chemically were not included. Also excluded were patients bleeding from carcinoma, esophageal varices, or other nonpeptic diseases.

Most of the patients who died were so ill that they could not eat or drink and thus did not receive the feeding treatment.

However one assesses the merits of these earlier reports,[29, 33] it is clear that most patients with bleeding from peptic ulcer disease can be fed and will benefit from such a program. Feeding cannot be utilized in that subgroup of bleeding patients who are continuously vomiting, nauseated, in shock, or who have ileus. This subgroup, however, constitutes the most difficult to treat (especially if they are in the older age group and have complicating health problems) and accounts for the bulk of deaths from bleeding duodenal ulcers.

Intragastric drip is a varient of the Meulengracht approach. Milk plus antacid is continuously dripped into the stomach in amounts of 2.5 to 3.5 liters per 24 hours. Ashby et al.[2] reported the use of this therapy in 425 patients thought to be bleeding from peptic ulcer. They added a Meulengracht diet to the drip regimen as desired by the patient. Patients with esophageal varices, pyloric stenosis, acute gastric dilatation, and ileus were excluded. More than a quarter of the patients were over 60 years of age. The overall mortality was 4.9 per cent. When patients in whom the tube could not be kept down during the first 12 hours (usually because of vigorous bloody vomiting) were included, the mortality rate rose to 6.1 per cent. In the group diagnosed as duodenal ulcer with hematemesis (200 patients), the death rate was 5 per cent.

A more pertinent and realistic view of the efficacy of milk-drip was provided by Scobie.[37] A comparison was made, within one institution, of results of milk-drip therapy on a surgical ward (69 patients) with results in a medical ward (76 patients) where milk-drip was not used. Patients were not randomly selected and the sites of bleeding within the upper gastrointestinal tract not fully defined. All patients required transfusions and the average blood transfusion requirements were similar in both groups. Emergency surgery was required in seven patients in each group. It was concluded that milk-drip therapy was of little, if any, benefit in the seriously bleeding patient.

It is evident that frequent, liberal feedings, the use of supplemental milk (or antacids), and intragastric drip techniques are associated with satisfactory cessation of bleeding in most patients. Whether this is due to the therapy or simply reflects the natural history of the disorder is still unclear. It should be remembered that even patients treated by the older method described briefly in the first sentence of this section, methods which are anathema to the modern physician, suffered a mortality rate of only 8 to 9 per cent.[28]

INTRAGASTRIC LAVAGE

Iced saline lavage is widely used in the treatment of active gastrointestinal bleeding. Most reports on alternate forms of therapy, whether the other treatments discussed in this article, intravascular delivery of drugs or clots, or emergency surgery, apply to patients who have failed to stop bleeding with the use of iced saline lavage. Iced saline lavage is

presumed to operate by decreasing gastric blood flow and increasing pH. The fluid can be chilled to 6 to 8° C by using ice generously, and copious amounts of fluid (perhaps up to 10 liters in 30 to 60 minutes) should be instilled. A large bore nasogastric tube or Ewald tube permits effective instillation of fluid and removal of clots; a double-lumen type[28] may be helpful. Instillation of the iced solution can be alternated or combined with the use of solutions to raise gastric pH. Although saline is the traditional fluid used, iced water is simpler, cheaper, and does not appear to offer any additional hazard.[5]

It is particularly difficult to offer any judgment concerning the efficacy of iced-fluid instillation. Obviously many patients do stop bleeding during such therapy. The universal acceptance of this form of treatment has precluded any reports detailing effectiveness beyond the anecdotal notation that patients either did or did not stop bleeding. Those that don't are considered "failures of usual medical therapy," and other forms of treatment are then used.

GASTRIC COOLING

Although the iced saline or water lavage which is widely used in upper gastrointestinal bleeding probably exerts its effect by cooling, the term gastric cooling is usually reserved for more formal attempts at lowering gastric temperature by the use of one of several types of gastric cooling machines. These machines consist of a refrigeration unit, a pump, a nasogastric tube, and an attached gastric balloon. A cooling mix (water-alcohol) is circulated in order to bring the temperature down to the desired range. Gastric cooling for upper gastrointestinal hemorrhage was first described by Wangensteen et al.[38] Subsequently the concept was extended to the use of gastric freezing as a definitive treatment for peptic ulcer disease. While gastric freezing has been abandoned, both because of its lack of lasting benefit and a high complication rate, gastric cooling for bleeding continues to have its adherents.[15]

The role of gastric cooling in upper gastrointestinal bleeding was reviewed in this publication a decade ago.[39] Cooling was recommended as an emergency procedure for serious bleeding. Circulating fluid temperatures of 0° C or above (compared with "freezing" temperatures of 0° C or below) is used for prolonged periods. The rationale for cooling is the demonstration in animals that gastric blood flow is reduced, gastric secretion and digestion inhibited, and pepsinogen release blocked. Presumably the decrease in blood flow allows initial cessation of bleeding, and the decreased secretion inhibits digestion allowing clots to form and healing to occur. The experience at the Columbia-Presbyterian Medical Center was reviewed.[39] Bleeding from a variety of upper gastrointestinal sites was controlled in 93 of 114 patients with severe bleeding. In the duodenal ulcer group (means of diagnosis not specified) bleeding was controlled in 13 of 16 patients. Although there was a favorable response in a large percentage of the patients, 54 died; five in the duodenal ulcer group. This emphasizes that mortality in gastrointestinal bleeding is influenced by many other factors than the immediate bleeding itself.

In 1966, Rodgers et al.[34] reported experiences at another New York City Hospital. Bleeding was controlled in 21 of 33 patients with upper gastrointestinal bleeding from various sites. In seven of ten patients with duodenal ulcer bleeding, cooling resulted in cessation of bleeding. Despite these apparently favorable results, the overall death rate was 52 per cent and three of the ten duodenal ulcer patients died. This report stressed the high complication rate associated with gastric cooling. These included pneumonia, septicemia, thermal damage, generalized body hypothermia, paralytic ileus, and mechanical difficulties with the unit. Although subsequent refinements of the apparatus should render mechanical problems less likely, it is clear that gastric cooling is not an innocuous procedure and that complications in the poor-risk, briskly bleeding patient in whom such an approach might be useful, are not inconsequential.

Since the early and mid-1960's, enthusiasm has waned and further reports are scanty. Cooling with modified units was attempted in two overseas centers.[3, 32] Sixty-four patients, 27 of whom had a duodenal ulcer, were treated with cessation of bleeding, either temporarily or permanently.

The experiences of Sandlow and Spellberg[36] were in contrast to the above studies. Fifty patients, all either in shock or difficult to maintain, were treated. Forty-six had received four or more units of blood in the preceding 24 hours. Cooling produced cessation of bleeding, at least temporarily, in 45 patients, but bleeding recurred in 25. In 16 patients with duodenal ulcer (means of diagnosis not specified), bleeding stopped, in six only temporarily. None of the duodenal ulcer patients died, but in the overall group 16 died (32 per cent). This figure was compared with the generally quoted overall mortality figure from all upper gastrointestinal bleeding of 8 per cent. Personal experience indicated a death rate of 40 to 50 per cent in bleeding patients with complications similar to the ones treated by cooling. Since this was an uncontrolled study, as were all the others cited, the validity of these comparisons is uncertain. Complications of aspiration pneumonitis, cardiac arrhythmias, and one instance of alcoholic intoxication from a leaking balloon (no other numbers given) were ascribed to the procedure.

Systemic hypothermia (as contrasted to local intragastric cooling) has also been advocated to treat bleeding duodenal ulcers.[17] This procedure requires intensive nursing care, the use of hypothermia blankets, ice packs to the axilla and groin, rectal thermocouples, and drugs to prevent shivering. Of 12 patients with massive gastrointestinal bleeding (not all from the upper tract), control was achieved in nine. The one patient with bleeding duodenal ulcer did not respond and four of the 12 died. Cardiac arrhythmias developed in seven patients, one of whom suffered cardiac arrest. Two developed pneumonitis and two severe paralytic ileus. Other experiences have been reported.[23, 41] The number of patients treated is small, the difficulties with the procedure have been emphasized, complications are many, but success (as is true for all modalities of treatment reported) does occur.

The wave of enthusiasm and interest in cooling as a means of therapy has waned. Despite some favorable results, cooling appears to be too

complicated, too uncertain, and fraught with too many hazards to offer much promise as a significant therapeutic technique in the treatment of duodenal ulcer bleeding (or, indeed, in upper gastrointestinal bleeding in general). Few institutions now employ this method and most cooling machines are gathering dust in storerooms. Systemic hypothermia has not produced any improvement over gastric cooling and is even more complicated and perhaps more hazardous to use.

LEVARTERENOL INSTILLATION

Levarterenol (norepinephrine) is a potent alpha-adrenergic vasoconstrictive agent. It is almost completely destroyed in one passage through the normal liver. When no collateral shunting of blood around the liver exists levarterenol is instilled into the stomach with little danger of systemic action.[19] Levarterenol (8 mg in 100 ml saline) is instilled into the nasogastric tube which is clamped for 30 minutes. The stomach is then irrigated to determine whether bleeding was stopped. Instillations are repeated 1 to 3 times with diminution and control of bleeding usually noted within three instillations. If successful, instillations are repeated every hour for 4 to 6 hours; every 2 hours for 4 to 6 hours; then progressively reduced and discontinued.[18] The drug has also been administered intraperitoneally (8 mg in 250 ml saline).[20]

In two papers published virtually simultaneously clinical and experimental data were presented.[19, 20] In dogs with an excised gastric mucosal defect, six of eight animals treated with gastric instillation of levarterenol survived and eight of nine with intraperitoneal instillation survived. Fifteen of 17 control animals died. In one paper the results in 18 patients with "severe upper gastrointestinal bleeding" (criteria for selection and previous attempts at therapy not mentioned) were treated. In 12 the bleeding ceased or became insignificant. Cases included bleeding from postoperative gastrectomy, stress ulceration, gastric cancer, and duodenal ulcer. In the second paper successful cessation of bleeding in 12 of 18 patients was again reported. Presumably, these are the same patients. Kiselow[18] reported use of levarterenol in 12 patients in whom treatment with intragastric iced saline had been unsuccessful. Hemorrhage was controlled in seven instances—a success rate of 54 per cent. Treatment was successful in one of the two patients with duodenal ulcer. In other patients with peptic ulcer disease success was achieved in one with pyloric ulcer and failure in two with gastric ulcers. An attached editorial by LeVeen indicates that the method may be most useful in nonpeptic ulcer bleeding (gastritis, stress ulcers, postgastrectomy bleeding). No untoward effects of levarterenol instillation were reported.

A more recent report[10] describes results in 12 patients with massive upper gastrointestinal bleeding (shock or blood loss of greater than 3 liters) and advanced malignant disease. In none was bleeding controlled with nasogastric intubage, iced saline lavage, or antacids, and one had continued bleeding despite selective intra-arterial injection with vasopressin. Cessation of bleeding occurred in 11 patients. Five eventually

rebled with three again controlled by reinstituting levarterenol lavage. Only two patients were definitely shown to have duodenal ulcer (although others may have)—bleeding stopped in both. Comparison with 12 other patients from the same hospital treated before and during the levarterenol trial, suggested that levarterenol was efficacious. Eleven of the 12 died with active bleeding, two of whom had duodenal ulcer. Only two of the 12 treated with levarterenol (neither with duodenal ulcer) died while actively bleeding.

An interesting experimental study on levarterenol instillations and cooling[40] has recently been published. In dogs, levarterenol in saline at 38° C produced a 10 per cent decrease in gastric blood flow when compared with saline (38° C). Saline instilled at 6.8° C produced a drop of 45 to 50 per cent compared to control saline. Adding levarterenol to cold saline produced a further drop of about 10 per cent.

If levarterenol exerts its effect through decreasing gastric blood flow, its action would seem to be of limited benefit compared with cooling. It may be that a significant local vasoconstrictive effect is not measured adequately by assessing total gastric blood flow. Such a local effect on small vessels may be reason why the action of levarterenol appears to be greater in diffuse bleeding produced by such disorders as hemorrhagic gastritis than it is for ulcer bleeding, where the vessels involved usually are larger.

CONTROLLED pH

Feeding, milk and antacid drip, nasogastric suction, iced saline lavage, and intragastric cooling all tend to decrease gastric acidity. Gastric pH has not, however, been continuously monitored in these situations. It is difficult to evaluate pH control in these forms of therapy. A report of meticulous control of pH in the control of upper gastrointestinal bleeding is therefore of interest. Curtis et al.[8] used a method which was simple and easy to apply in ordinary bedside situations. The contents of the stomach were aspirated and the pH measured with phenaphthazine paper (Nitrazine). Sixty ml of antacid was instilled, allowed to mix in the stomach for 15 minutes, and the stomach again aspirated. If the pH was below 7.0, additional antacid was instilled and the process repeated until the pH of the gastric aspirates was neutral. Thereafter, antacid was given hourly (following aspiration) to maintain neutrality. The amounts of antacid used, obviously, are not significant; the important point being to ensure the neutrality of the gastric contents. Hemorrhage stopped in 23 of 25 patients, three with bleeding duodenal ulcer. In one ulcer patient bleeding could not be controlled and the pH could not be raised above 4.5 even with the instillation of 200 ml of antacid every 15 minutes. The other failure was in a patient with pulmonary embolus being treated with thrombolytic therapy. In 17 of the patients in whom bleeding was controlled, no further therapy was needed. Five died, however, of various causes (metastatic disease, renal failure, sepsis, pulmonary failure). Six patients with controlled bleeding underwent elective surgery, including one with duodenal ulcer.

Meticulous control of gastric pH seems attractive because it is simple and without hazard. The experience in control of hemorrhage appears to be favorable. The high death rate despite adequate control of hemorrhage emphasizes a recurrent theme in discussions of massive gastrointestinal bleeding, i.e., mortality is influenced by many factors other than the bleeding itself.

ENDOSCOPIC CONTROL TECHNIQUES

The development of modern fiberoptic endoscopic equipment has spurred interest in the control of gastrointestinal bleeding by introduction of chemical or physical agents through the endoscope to the bleeding lesion. A variety of approaches have been suggested for investigation including the use of tissue adhesives, the application of hemoclips, or the direct instillation of agents such as levarterenol or sclerosing fluids.

Various thermal agents (electrosurgery, laser photocoagulation, and cryosurgery) are being actively studied in a number of centers. The first two have been applied in man. Before reviewing briefly the available clinical experience it is necessary to emphasize the many problems which exist. Optimal equipment requirements have not been determined, the manner in which such equipment should be used (such as power settings, distance from the lesion, and kinds of laser) is far from clear, and, perhaps more importantly, whether tissue damage may limit the usefulness of these approaches is an unsettled issue. Hazards to the operator, especially with laser techniques, also present real problems. Endoscopic thermal therapy for bleeding should not be used by the ordinary, even if skilled, endoscopist, but should be reserved for trial in selected research centers where the effectiveness and problems of these modalities can be properly evaluated.

Reported clinical applications are relatively few. Papp[31] briefly reported the results of electrocoagulation in 25 patients. There was initial control in 21 patients, four of whom subsequently rebled. In the nine duodenal ulcer patients one bleeding vessel was missed and two others rebled. Gaisford[13] utilized electrofulguration in 20 patients[13] in whom the exact site of disease was localized. Permanent hemostasis was achieved in 18 patients, two with bleeding from duodenal ulcers. Even in the two patients (both with gastric ulcer) in whom permanent hemostasis was not achieved, there was sufficient temporary control so that both were operated on under normovolemic conditions. Isolated experiences in three patients had previously been reported.[4, 42] None had duodenal ulcer, but in all the method was, at least temporarily, successful.

The use of endoscopic laser to control gastrointestinal bleeding in humans has also been reported.[11, 12] Successful results were briefly reported in 13 patients with a variety of upper and lower gastrointestinal lesions. Most had a bleeding duodenal ulcer.

The subject of endoscopic control of gastrointestinal bleeding was recently reviewed.[16] The potential impact of these methods of control is

exciting but many technical matters are not yet resolved; the procedures are complex and there are many unanswered problems concerning hazards and indications for use.

MISCELLANEOUS

Bentonite is a clay earth mineral effective in preventing the activity of gastric and duodenal proteolytic enzymes.[30] A purified preparation was utilized in the treatment of bleeding from peptic ulcer.[1] Treatment consisted of emptying the stomach by aspiration and then instilling 30 to 40 ml bentonite suspension every 1/2 hour for 2 to 7 days. Therapy was discontinued, unless obviously successful, once aspirates were clear and hemoglobin was stable without further transfusions. No food, milk, or antacids were used during bentonite therapy since they interfered with the proteolytic-inhibiting properties. In an initial trial in 24 patients selected because acute operation was contraindicated, hemostasis was achieved at least temporarily in 19. A second group of 93 patients, comprising a consecutive series with hematemesis and melena, were also treated. It was the author's judgment that 74 of these would previously have come to emergency operation. Of the 93 patients, bleeding was controlled in 79. Thirty-four of these subsequently were operated electively, well controlled and prepared. All patients had gastric or duodenal ulcer bleeding. The analysis of cases in this report is confusing and it is difficult to state the overall mortality. Further studies on this agent have apparently not been reported.

Carbazochrome salicylate (Adrenosem), a drug which is said to act by influencing capillary permeability without affecting heart rate or output, blood pressure or clotting, was used in the treatment of 17 personal consecutive cases of massive gastrointestinal bleeding.[9] The drug was given intramuscularly, 10 mg every 2 hours. In all cases bleeding was successfully controlled; immediately in 88 per cent and within 24 hours in 12 per cent. There were no failures. Nine patients had duodenal ulcer. No rebleeding or complications of therapy occurred. Details of other therapy, except that cooling was not used, were not given. Some were later operated, but no complete breakdown was given. This is a truly remarkable report. One wonders what has developed in the last 6 years since no further reports seem to have appeared and the current *Physicians' Desk Reference* (1975) does not contain any listing for carbazochrome. A later trial of the drug in aspirin-induced gastric mucosa injury in rats failed to demonstrate any beneficial action but instead demonstrated that carbazochrome salicylate enhanced the injury.[22]

The application of circumferential pneumatic compression using a "G" suit has been advocated as an aid in the control of upper gastrointestinal bleeding, as well as in intra-abdominal bleeding in general. Only isolated instances of its use have been reported and it is not clear whether the mechanism of reported success involves mainly shifts of blood from infradiaphragmatic structures toward the heart, thus tending to correct hypovolemic hypotension, or whether direct tamponade of the bleeding site also occurs.[14, 26]

Based on observations[7] that plasminogen activator and free plasmin were present in gastric venous blood in a greater proportion of patients with peptic ulcer disease than in a control group, thus implicating a possible fibrinolytic factor in upper gastrointestinal hemorrhage, a trial of an antifibrinolytic agent, tranexamic acid, was undertaken.[6] In the group in whom subsequent roentgenograms indicated the presence of peptic ulceration there was no difference in failure rate between the treated patients and those receiving placebo. A statistically significant benefit was, however, found in those with negative roentgenographic findings—presumably patients bleeding from gastric erosions.

A most exciting new approach to the treatment of upper gastrointestinal bleeding involves the use of specific H_2-antagonist drugs. These agents act to increase gastric pH by antagonizing the action of many stimuli to acid production. The site of action is presumed to be at a final step involving histamine. Metiamide (a drug which has now been withdrawn from trial because of bone marrow toxicity and is being replaced by cimetidine) was used successfully to treat 14 bleeding episodes in 11 patients.[21] The bleeding was either due to errosive gastritis or to duodenitis in nine patients and to bleeding from duodenal ulcer in two. In two other patients with ulcer bleeding, both with ulceration into major vessels, control was not achieved. This is obviously a preliminary report but clinical trials in progress on the use of cimetidine in the treatment of many aspects of ulcer disease, and its use in upper gastrointestinal hemorrhage should clarify the role of this new class of drugs.

A PERSONAL PERSPECTIVE

On the basis of published reports as well as personal clinical experience it seems worthwhile to offer some recommendations. These are neither infallible nor even necessarily correct. For the reasons enumerated at the beginning of this review, any set of recommendations is necessarily highly subjective.

The initial approach to nonsurgical management first requires identification of the severity of bleeding. Whether exact identification of the bleeding site by early endoscopy aids in therapy remains an unsettled issue and the decision as when to use this technique is a matter for individual judgment. For most patients without hematemesis and who are hemodynamically stable, early feeding is indicated, usually well-tolerated, and associated with clinical improvement. It seems reasonable (although certainly not essential) that the feeding be relatively bland. Frequency of feeding (whether food or antacid) to help control pH and relatively small quantities of food at any one time (to decrease acid stimulation and to decrease the likelihood of vomiting) also seem desirable. I use this form of therapy throughout the entire 24-hour period. Whether frequent awakening is less disturbing than the placement of an intragastric tube to permit continuous drip is an individual decision reached by physician and patient. I try to keep the patient relatively quiet and free from additional stress—conditions difficult to achieve in the modern hospital and virtually impossible to achieve in most intensive care units. Mild sedation may be helpful.

In the more seriously bleeding patient no medical or surgical therapy yet described is uniformly beneficial or universally accepted. These patients should have an intragastric tube in place both to permit monitoring and to allow delivery of therapeutic agents. Vigorous ice-water lavage carried out through a large-bore, double lumen tube should be used. It is essential that the water be as cold as possible and continuously emptied from the stomach. If bleeding does not lessen after an initial period of lavage (difficult to define, but perhaps 30 to 60 minutes), then a trial of 1 to 3 instillations of levarterenol can be undertaken. If bleeding does stop, then intragastric drip, attempting to control pH, interspersed with periods of suction and lavage, can be started. The failure to stop bleeding with these methods should be a signal that medical management has failed and that angiographic or surgical methods should be tried. None of the other medical therapies presently available offer a clear advantage over this program, although occasionally (as noted in the review) each of these methods will work when this program has apparently failed. The advantage of this program is that it is easy to apply, requires no special equipment, or expertise, and, most importantly, seems just as likely to be successful as any other program. Exactly how and when to decide that medical therapy has failed is a difficult and individual decision. Undue persistence with any method may create additional hazards.

The role of direct endoscopic attack on the bleeding lesion and the possible place of newer, specific drugs like the H_2 antagonists remain to be defined. They offer hope that future therapy in severe bleeding ulcer problems may be more successful than that presently available.

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Surgical Management of Actively Bleeding Duodenal Ulcer

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The objectives of an operation for bleeding duodenal ulcer are to control hemorrhage and eliminate the ulcerogenic mechanism with minimal morbidity and mortality. To achieve this goal some surgeons have favored gastric resection with or without vagotomy; others have preferred the more conservative approach of a vagotomy, oversewing of the bleeding site, and pyloroplasty. The purpose of this discussion is to examine the advantages, disadvantages, and results of each approach.

Some institutions serve large veterans' groups, others an indigent population, and still others a private referral practice, all factors which may influence the selection and results of an operative procedure. The results of any series should be evaluated keeping in mind the population treated.

Active Bleeding.

Patients who are actively bleeding and considered as candidates for surgical correction are usually divided into two groups: massive and continuing bleeding.

Authors will differ on the precise definition of massive bleeding, but most would agree with the criteria of Cammock et al.[3] which require the presence of one of the following conditions: (1) blood loss estimated at more than 1000 cc per 24 hours or greater than 30 per cent of estimated blood volume; (2) admission hematocrit of less than 28 per cent; (3) transfusion of more than 1500 cc of whole blood per 24 hours required to maintain homeostasis; and (4) hypotension or clinical shock secondary to blood loss.

Even the above are but general guidelines, and most would argue today toward earlier operation, especially for: (1) patients who have bled previously and require hospitalization and transfusion; (2) patients with a known rare blood type; (3) elderly patients or those with concurrent illnesses which significantly increase surgical risk; and (4) recurrent in hospital bleeding after cessation of medical management.

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Conversely, some patients with massively bleeding duodenal ulcers have systemic illnesses in which surgery would be contraindicated; examples being intractable heart failure, end stage cirrhosis, terminal neoplastic disease, and severe pulmonary insufficiency. Some of these patients may be candidates for the newer methods of nonoperative management of controlling bleeding duodenal ulcer.

Operation is considered to be urgent when performed on the actively bleeding patient whose condition has become stabilized by whole blood and body fluid volume replacement. Operation is considered to be an emergency when the patient has been in shock and continues to bleed.

Diagnosis

Diagnosis is reviewed in another section of this volume, and I agree with those who do not favor emergency roentgenographic upper gastrointestinal studies. Snyder and Stellar[26] did not find such studies an aid in treatment of 77 patients with bleeding duodenal ulcer, and Vogel[28] found them to be only partially successful.

Fiberoptic endoscopy following gastric lavage and removal of clots by a skilled endoscopist is diagnostically accurate and, when coupled with skilled selective angiography in difficult cases, can result in a high degree of accurate identification of the bleeding site.

The more accurate the diagnosis preoperatively, the shorter, less traumatic, and safer will be the surgery.

Operation

The choice of an operation for upper gastrointestinal bleeding from duodenal ulcer continues to be debated between those who favor gastric resection with or without vagotomy and those who prefer vagotomy, oversewing of the bleeding point, and pyloroplasty or drainage procedure. The factors to be evaluated include:

MORTALITY. In evaluating selective vagotomy and oversewing of the ulcer and pyloroplasty, Jensen and Guldberg[17] experienced an 8 per cent operative mortality. Farris and Smith[13] recorded a 6 per cent mortality in patients undergoing truncal vagotomy, oversewing, and pyloroplasty. Evaluating the same procedure, Klingensmith and Oles[18] and Vogel[28] found mortality rates of 2.4 per cent and 6.7 per cent respectively. Foster, Hickok, and Dunphy,[14] while setting out to disprove the value of the procedure of vagotomy, oversewing, and drainage, were able to show a decrease from 30 per cent mortality when gastrectomy was employed to 8.7 per cent for the more conservative procedure. Buckingham and ReMine[2] and Brooks et al.[1] reported a mortality of 11 per cent in their patients. Snyder and Stellar,[26] operating only on patients who at some time preoperatively were in shock or had lost 50 per cent of their estimated blood volume, had a 17 per cent operative mortality employing vagotomy, oversewing, and pyloroplasty.

The higher mortality rates for gastric resection with or without vagotomy are a reflection of more extensive surgery in high risk patients. Thorne and Nyhus[27] reported a mortality of 23 per cent in their

patients undergoing vagotomy with resection. Foster, Hickok, and Dunphy[14] reported a 32 per cent mortality rate in patients treated by gastrectomy; Darin, Polacek, and Ellison[8] reported 25 per cent mortality in their patients. Palumbo and Sharpe,[22] utilizing vagotomy and antrectomy, experienced a 4.5 per cent mortality, a rate much lower than in other reported series.

Recently, Hines[16] has summarized the comparative mortality of the two procedures as reviewed by Crook et al.,[7] finding an average mortality of 20 per cent with vagotomy, oversewing, and gastric resection; for vagotomy, oversewing, and pyloroplasty the figure is 10 per cent (Table 1).

REBLEEDING. With all operations rebleeding may develop at varying times postoperatively. Jensen and Guldberg[17] found a 16 per cent incidence of rebleeding following selective vagotomy, oversewing, and pyloroplasty. Farris and Smith[13] noted an 8 per cent incidence of rebleeding following vagotomy and pyloroplasty as compared to a 9 to 20 per cent incidence of rebleeding following gastrectomy.[12] Snyder and Stellar,[26] performing vagotomy, oversewing, and pyloroplasty on a group of patients with massive bleeding, observed rebleeeding in 10 per cent of patients; Vogel[28] reported 4.4 per cent with rebleeding following the same procedure. Brooks, Kia, and Membreno[1] had a 7.5 per cent incidence of rebleeding for a similar procedure.

Following vagotomy and antrectomy, Palumbo and Sharpe[22] found a 3.7 per cent incidence of early rebleeding and 0.6 per cent of late rebleeding. Farris and Smith,[13] in reviewing the frequency of rebleeding following subtotal gastrectomy in nine different series reported in the literature, found a range of 5.9 to 30 per cent. Leap and Welch[19] observed a 14 per cent incidence of rebleeding following gastrectomy.

Hines,[16] in a review of the problem of rebleeding, observed a range of 8 to 33 per cent in patients undergoing gastrectomy; the range was 5 to 26 per cent with an average of 15 per cent for patients undergoing vagotomy and pyloroplasty (Table 2).

Table 1. *Operative Mortality*

GASTRIC RESECTION	PER CENT	VAGOTOMY AND PYLOROPLASTY	PER CENT
Thorne and Nyhus[27]	23.0	Jensen and Guldberg[17] (selective vagotomy)	8.0
Foster, Hickok, and Dunphy[14]	32.0	Farris and Smith[12]	6.0
Darin, Polacek, and Ellison[8]	25.0	Klingensmith and Oles[18]	2.4
Palumbo and Sharpe[22] (vagotomy and antrectomy)	4.5	Vogel[28]	6.7
Hines and Wilkolm[16] (Review average)	20.0	Foster, Hickok, and Dunphy[14]	8.7
		Buckingham and ReMine[2]	11.0
		Brooks, Kia, and Membreno[1]	11.0
		Snyder and Stellar[26]	17.0
		Hines and Wilkolm[16] (Review average)	10.0

Table 2. *Rebleeding*

GASTRIC RESECTION	PER CENT	VAGOTOMY AND PYLOROPLASTY	PER CENT
Palumbo and Sharpe[22] (vagotomy and antrectomy)	4.3	Jensen and Guldberg[17] (selective vagotomy)	16.0
Farris and Smith[13] (Review range)	9 to 20	Farris and Smith[13]	8.0
Leap and Welch[19]	14	Snyder and Stellar[26]	10.0
Hines and Wilkolm[16] (Review range)	8 to 33	Vogel[28]	7.5
		Hines and Wilkolm[16] (Review range)	5 to 26

RECURRENT ULCERATION. There is general agreement that vagotomy and hemigastrectomy has the lowest rate of recurrent ulceration varying from 0 to 2 per cent.

Recurrence after vagotomy, oversewing and drainage procedures will vary from 5 to 10 per cent or more, depending on the length of follow-up.

OTHER SIDE EFFECTS AND METABOLIC SEQUELAE. Other complications accompanying these operative procedures may not appear for several months and even years after surgery. It is important that these be mentioned, since they are often overlooked and should be included as factors that govern decision.

The reported incidence of severe dumping in postgastrectomy patients is of the order of 10 per cent, and while it is also present in vagotomy and pyloroplasty, it is less frequent and more easily controlled by dietary measures. Diarrhea may occur after either procedure, but is not disabling in more than 1 or 2 per cent of patients.

Although the true incidence of bile vomiting is unknown, it is more frequently observed after a Billroth II procedure. For patients who are accurately diagnosed and have severe symptoms, a simple Roux-en-Y diversion of bile and pancreatic content of the afferent limb end-to-side into the efferent limb 30 cm below the gastrojejunostomy is usually curative.[10]

The weight loss following hemigastrectomy occurs more frequently and is more severe[29] than that after vagotomy and pyloroplasty.[24]

While iron deficiency anemia is more common after gastrectomy,[9] it is also found after vagotomy and pyloroplasty if the patients are followed long enough.[4]

Osteomalacia is detectable in 20 to 30 per cent of postgastrectomy patients,[11] but has not been reported as a complication of vagotomy and drainage procedure.

Technical Considerations

Vagotomy, gastrectomy, and pyloroplasty each involve technical problems such as incomplete vagal sectioning, gastric retention, or stump blowout.

Satisfactory control of the ulcerogenic mechanism can be accomplished only with a complete vagotomy. Surgeons may become complacent about truncal vagotomy and leave fibers at the cardioesophageal junction intact. Crile[5, 6] illustrated and described the technique of stripping the fibers with a special wire loop. Hallenbeck et al.[15] recently reemphasized the importance of clearing all the "criminal" nerves at the cardioesophageal junction with striking reduction in the incidence of recurrent ulceration in a group of patients who had proximal gastric vagotomy. This procedure is not difficult technically but requires identifying and clearing the anterior and posterior vagal trunks completely from the cardioesophageal junction and up onto the esophagus an additional 5 to 7 cm.

In ligation or oversewing of a bleeding ulcer, the surgeon may be greatly relieved when his initial sutures control the hemorrhage; however, the area of bleeding should then be scraped with a sponge to make certain hemostasis is secure. To lessen the concern of incorporating any portion of the common bile duct in the ligation, I prefer to place the ligation in backhanded fashion, running the needle point in a medial and upward direction rather than lateral and downward as would be usual for a right-handed surgeon.

In gastrectomy, most of the serious problems involve the duodenal stump. A secure stump closure is facilitated by proper mobilization and a multilayered closure of viable bowel wall layers. The newer automatic stapling devices accomplish this readily and may be reinforced by a final layer of interrupted nonabsorbable suture. If any doubts remain about the stump, a T-tube catheter placed laterally in the second portion of the duodenum will vent any build-up of pressures in the afferent limb.

Although a proximal gastric vagotomy of the treatment of duodenal ulcer is presently undergoing widespread investigation in the United Kingdom and in this country, there is insufficient information on this procedure in the treatment of active bleeding at this time.

Comments

A surgeon's training, experience, and flexibility in approach to the individual patient will determine which operation he will choose for bleeding duodenal ulcer. The advantages and disadvantages of each procedure have been reviewed.

All would agree that patients who are operated on early do better than those who have had significant blood volume replacement. This should be especially true of the elderly; patients over 60 do have a poorer response to massive hemorrhage because associated disease decreases their capacity for withstanding stress.

Although no operation is ideal, there may be renewed interest in the nonoperative management of bleeding and nonbleeding duodenal ulcer. MacDonald and co-authors[21] have reported striking success in the management of stress bleeding using the hydrogen ion antagonist metiamide. Similarly, Longstreth and associates.[20] using cimetidine, an H_2

receptor antagonist, were equally enthusiastic about eliminating nocturnal pain, hypersecretion, and establishing nocturnal anacidity in a group of ulcer patients. Eisenberg and Speer[11] employed an intraarterial method of embolizing autologous clot to control pyloroduodenal hemorrhage in a group of patients with severe associated disease and considered too ill for surgery.

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End of Article 7A

Considerations in the Management of Perforated Peptic Ulcers

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Acute perforation of a peptic ulcer may be a life-threatening abdominal catastrophe that in usual circumstances can be easily diagnosed and treated. The etiology of perforated duodenal ulcers is unknown, but stress, alcohol, and salicylates have been implicated. Thirty to 50 per cent of patients with perforated duodenal ulcers have no history of duodenal ulcer disease or ingestion of alcohol or salicylates. Most perforations occur a few hours after meals, and whether gastric hypersecretion is important is unknown. Treatment can be medical or surgical depending on the patient's age, duration of perforation, previous ulcer symptoms, and general medical condition.

As in other types of surgery, the best approach is individualized, so that treatment effectively alleviates the problem and yields the best long-term results with minimal morbidity and mortality.

We review the clinical presentation, diagnosis, and treatment of perforated peptic ulcer. Criteria that determine which operation should be done for a perforated peptic ulcer are presented.

CLINICAL FEATURES

The typical feature of a perforated ulcer is the abrupt onset of severe epigastric pain that causes the patient to seek prompt attention. Often the exact time of perforation can be recalled by the patient. Most perforations occur in men; the male-to-female ratio ranges from 2.5 to 1[14] to 10 to 1.[19] The mean age at the time of perforation in adults has ranged from 43[6] to 56 years,[14] being somewhat higher in females. Perforations in neonates are uncommon.

Perforations occur most frequently in the late afternoon;[12] a delayed diagnosis and higher mortality occur at night.[2] Throughout the world, perforations occur most commonly on Friday and least commonly on Sunday, except in Israel where the incidence is lowest on Saturday.[12] This shows that this acute surgical condition applies to whatever day

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the "day of rest" is observed. Atypical presentations do occur. In elderly patients, those who are seriously ill with other diseases, or patients with spinal cord injuries, pain may not be a major feature. Because of this, the diagnosis may be delayed in these patients and the mortality rate is higher. In other patients, pain may be localized to one area of the abdomen and an incorrect diagnosis of cholecystitis, appendicitis, perforated colonic diverticula,[19] or pancreatitis may be made, again delaying the diagnosis and increasing morbidity and mortality.

DIAGNOSIS

Physical findings depend on the time of presentation after perforation. Usually the abdomen is rigid with direct and rebound tenderness, and loss of hepatic dullness can be elicited. A history of abrupt onset of epigastric pain with a board-like abdomen and loss of hepatic dullness should make one suspect a perforated ulcer. The definitive diagnosis is made by the presence of pneumoperitoneum. Three roentgenograms may be helpful. These are (1) a left lateral decubitus film, (2) an erect chest film, and (3) a supine view of the abdomen. Using these views pneumoperitoneum will be detected in 60 to 82 per cent[4, 11, 19] of patients. The left lateral decubitis view (left side down on the table) may demonstrate as little as 1 cc of free air. The erect chest film must be taken after the patient has been in an upright position for 10 to 20 minutes to allow the intraperitoneal air to be detected under the diaphragm. The plain abdominal film may show air outlining the bowel wall.[16] If roentgenographic diagnosis is uncertain, air or gastrografin can be injected into a nasogastric tube to increase the amount of intraperitoneal air or identify the site of perforation. Gallstones seen on the abdominal flat plate may confuse the correct diagnosis and this has led to an increased mortality in one series.[14] Laboratory tests do not help confirm the diagnosis, and sometimes treatment is delayed because laboratory findings suggest other diagnostic possibilities. For example, an elevated serum amylase may lead one to suspect acute pancreatitis. The leukocyte count is of little help, and in one series[19] it was normal in 80 per cent of patients. When the diagnosis is uncertain, the patient is observed for up to 6 hours during which time fluid, electrolyte, and colloid replacement therapy is accomplished. Since a delayed or missed diagnosis has a higher mortality, vigorous and accurate evaluation is mandatory to minimize morbidity and mortality.

TREATMENT

In all patients initial treatment consists of intravenous fluids, nasogastric decompression, and correction of fluid and electrolyte abnormalities. Third space fluid sequestration can be considerable and this should be corrected prior to surgery.

Antibiotics

The incidence of positive peritoneal cultures increases as the time from perforation is prolonged. In one series there were 21 per cent positive cultures at 6 hours, 30 per cent positive at 12 hours, and 63 per cent positive at 24 hours.[4] Streptococci and E. coli were the most common organisms cultured.[4, 19] Since intraperitoneal and wound infections account for a large percentage of postoperative morbidity, the use of antibiotics appropriate for streptococci and E. coli preoperatively might be of value. These antibiotics are continued for at least the first 2 or 3 days postoperatively and then discontinued if cultures are reported negative. Appropriate changes in antibiotics are made on the basis of the culture and sensitivity reports if the patient remains septic or the degree of peritoneal soilage was significant.

Specific treatment of the perforation then consists of other nonoperative or operative methods.

Nonoperative Treatment

Nonoperative treatment of perforated ulcers consists of nasogastric intubation, intravenous fluids, antibiotics, and close observation. Although formerly a popular method, not more than 10 per cent of perforations are treated this way today. This treatment is presently used in two situations: (1) A forme-fruste ulcer; a perforated ulcer that leaked into the peritoneal cavity but was sealed by omentum or surrounding tissues, and (2) in patients with other serious illnesses where the risk of surgery is prohibitive. In patients with acute medical illnesses where the operative risk is great, as in acute myocardial infarction, continued close monitoring of patients must be done and if peritoneal signs progress, laparotomy must be undertaken despite the high risk. Although satisfactory results have been reported using this treatment today, most surgeons have reserved it for the high risk moribund patients, for perforations discovered late, or for sealed perforations. The mortality rate for this treatment ranges from 50 to 100 per cent.[2, 19] These figures reflect patient selection rather than treatment methods as higher risk candidates are observed and a more favorable group undergo surgery.

Operative Treatment

Operative treatment is generally regarded as the best treatment for most patients with a perforated peptic ulcer. The therapeutic dilemma exists when deciding which operation should be done, i.e., simple suture plication or a definitive ulcer operation. If the latter option is chosen, one must then decide which operation should be selected. These alternatives are many and include vagotomy (truncal or selective) with drainage, vagotomy (truncal or selective) with resection, or as more recently suggested, proximal gastric vagotomy, or even subtotal gastric resection. To understand why definitive ulcer surgery might be needed in some patients and to try to identify the patient in need of this surgery, it is helpful to review the results of simple plication of duodenal perforations.

PLICATION OF PERFORATED ULCERS. In many reports plication has been the procedure of choice. It can be accomplished quickly and accurately and with minimal operating time. The perforation may be sutured directly, sealed with omentum, or both. Mortality rates following this treatment have ranged from 2.9 to 10 per cent.[1, 14] When plication is used as primary treatment, the mortality rate in most series is less than 10 per cent. High mortality rates usually reflect delayed diagnosis, co-existing medical diseases, or both. The higher mortality rates are usually reported in series where good risk patients are assigned definitive operations leaving the high-risk, sicker patient for plication. This no doubt explains the 21 per cent mortality rate in Jordan's series[9] where most perforated ulcers were treated by definitive ulcer surgery. Most deaths occur in patients with multisystem disease and in elderly patients. Jordan et al.[9] noted that the mortality rate in an otherwise healthy patient, younger than age 50, was less than 1 per cent with all types of surgical therapy. McEwan and Milligan[15] noted that three factors increased the operative morbidity and mortality after plication of perforated peptic ulcers. These include (1) patients over 50 years of age, (2) associated medical disease, (3) a delay of more than 6 hours between the time of perforation and the time of surgery. According to other reports,[2, 3, 17] when surgery was delayed more than 12 hours, the mortality rates were significantly increased.[2, 3, 17]

LONG-TERM RESULTS. Critical data on the natural history of ulcer disease after successful treatment of perforations have been obtained from several reports. In general, after simple plication one third of patients will require additional surgery, one third can be managed on medical therapy, and about one third will be asymptomatic. McDonough and Foster[14] noted that 75 per cent of their patients needing additional surgery after simple closure had the operation within the first 2 years after perforation. In their series, 23 per cent of patients followed 1 to 11 years after closure of the perforation required surgery to control the complications of peptic ulcer disease. In a collected series totalling 356 patients followed 4 or more years after plication,[4, 13, 19] 40 per cent required surgery, 28 per cent were asymptomatic, and 32 per cent were managed by medical therapy. Griffen and Organ[5] recently noted that 48 per cent of their patients followed from 2 to 27 years after plication for perforated ulcer either died of ulcer complications, required surgery, or required medical therapy for their ulcer symptoms.

WHO WILL NEED SURGERY? If the 30 to 40 per cent of patients who will require subsequent ulcer surgery could be accurately identified at the time of perforation it would be advantageous to perform a curative operation at that time. Mason et al.[13] followed perforated ulcer patients from 4 to 7 years. In patients with preperforative symptoms of less than 1 month, only two of 15 required subsequent surgery; 12 of 23 patients with symptoms longer than 1 month required reoperation. Mean basal and maximal acid outputs on the 7th to 10th postoperative day after simple closure were similar in both groups. They advised immediate definitive surgery for patients with chronic ulcers. In studying the importance of a history of ulcer disease, Greco and Cahow[4] noted that 45.7

per cent of patients with a chronic ulcer required further surgery, but only 15 per cent with an acute ulcer had surgery at 5 or more years of follow-up. In addition, 61 per cent of patients without a previous ulcer history remained asymptomatic compared to 32 per cent with an ulcer history. They noted that men, between the ages of 40 and 64 years, with a past history of ulcer disease (at the time of perforation) had a significantly higher probability of requiring subsequent surgery (65.7 per cent) as opposed to other patients (18.4 per cent). McDonough and Foster[13] noted that surgery was required later if symptoms were present 3 or more months prior to perforation. They too believed that patients between the ages of 50 and 70 years with previous ulcer symptoms 3 or more months prior to perforation were at risk. Excluding these patients only 25 per cent of the remaining group had further difficulties after plication. In contrast, Wangensteen et al.[19] reported no statistical differences in the incidences of patients requiring subsequent surgery when comparing patients with symptoms of less than 3 months' duration with those of more than 3 months' duration. Therefore, although it is difficult to predict with certainty the subgroups that will require further surgery, a definitive operation should be considered for middle-aged men with a history of ulcer symptoms who have had perforation less than 12 hours before operation, who have no evidence of major intraperitoneal sepsis, and who can tolerate the additional operative time. We believe that all other patients should be treated by plication of the perforation.

DEFINITIVE SURGERY FOR PERFORATED PEPTIC ULCER. If a curative ulcer operation is planned, several options are available. These include vagotomy and drainage, vagotomy and resection or subtotal gastrectomy and closure of the ulcer with proximal gastric vagotomy. The operation selected should be the one that has given the surgeon the best results with minimal morbidity and mortality. This obviously depends on the surgeon's experience and preferences and the patient population he is dealing with. The mortality rate after pyloroplasty and vagotomy for perforated peptic ulcer ranged from 1.1 to 5.5 per cent in four reports[6, 10, 12] totalling 783 patients. An operative mortality from 0 to 12.2 per cent was noted in three reports of 138 patients having either vagotomy and pyloroplasty and/or gastrectomy. In two series of patients treated by gastrectomy with or without vagotomy, the mortality rates were 15 per cent and 2.2 per cent.[9, 17] The long-term satisfactory results are approximately the same as when these operations are done for other surgical indications of peptic ulcer disease. However, as noted by Jordan et al., hemigastrectomy and vagotomy as a means of definitive therapy for perforated peptic ulcers should be considered in a relatively young healthier group of patients with a history of peptic ulcer disease. An argument against definitive ulcer surgery, particularly in patients without a history of ulcer disease, has been the unpredictable sequelae that may follow truncal vagotomy. Parietal cell vagotomy has certain theoretical advantages over truncal vagotomy and Johnston et al.[8] first reported the use of parietal cell vagotomy in five patients with perforated peptic ulcer in 1973. We have no experience with this operation

Table 1. *Comparison of Plication and Definitive Operations in the Treatment of Perforated Duodenal Ulcers*

		PLICATION OPERATIONS				DEFINITIVE OPERATIONS			
AUTHOR	YEAR	No. of Patients	Operative Mortality	Follow-up	Satisfactory Results	No. of Patients	Operative Mortality	Follow-Up	Satisfactory Results
Reimers	1967	94	5.3%			91	7.7%		
Hinshaw	1968					180	1.1%		
MacHayya	1968					73	4.0%	1–6 yr.	92%
Herbert	1969	100	0%			100	2%		
Donaldson	1970	297	9%	1–18 yr.	43%				
Khan	1970					81	0%	0.5–3.5 yr.	97.6%
McEwan	1970	189	4.7%			49	1.22%		
Booth	1971	332	2.9%						
Cohen	1971	687	7.9%						
McDonough	1972	158	10%	1–11 yr.	61%				
Wangensteen	1972	89	2.2%	6–21 yr.	20%	37	2.7%		97%
Greco	1970	297	5.5%	5 yr. or more	32%				
Jordan	1974	306	3.9%	0.3–22 yr.	27%	535	2.2%		86.8%
Griffin	1976	122	6.5%	2–27 yr.	52%	52	9.6%		

in acute perforation. We believe that if a definitive operation is done, the surgeon should employ the one with which he is most familiar and proficient. As yet there is no perfect elective operation for peptic ulcer disease; the same certainly applies for definitive surgery done for an acute perforated peptic ulcer.

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End of Article 8

Obstructing Duodenal Ulcer

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Gastric outlet obstruction, secondary to pyloric stenosis, in my experience, is the second most common indication for surgery in duodenal ulcer disease. According to several reports, the incidence of obstruction as an indication for surgery ranges from 11 to 30 per cent, depending on the patient population and on the incidence of elective versus emergency operations.[4, 8, 10, 12] In almost all series of cases, intractability of the disease to medical management is the most frequent indication for surgery in from 45 to 60 per cent of patients. Hemorrhage, the other frequent reason for surgery, is the principal indication in from 20 to 30 per cent of patients. In many patients a combination of indications may exist: a long history of episodic or recurrent ulcer pain, one or two episodes of melena, and the development of incomplete gastric emptying and nausea with occasional vomiting, making the indentification of any single indication for surgery difficult or inexact.

PATHOGENESIS

Gastric outlet obstruction occurs during the course of duodenal ulcer disease because of recurrent episodes of ulceration and inflammation in the pyloric channel or duodenal bulb, followed by healing of the ulcer and the deposition of scar tissue. Over a period of 10 or 15 years, with repeated episodes of duodenal ulceration, healing, and fibrosis, the pyloric channel or duodenal bulb becomes relatively scarred and stenotic with increasing gastric outlet obstruction. An active ulcer crater is frequently, but not always, present. In most patients, the gastric outlet obstruction is incomplete and some food, gastric juice, or ingested barium by roentgenography can be demonstrated to leave the stomach slowly. In a few patients, however, the gastric outlet obstruction may become complete. In some patients, because of persistent or chronic gastric stasis, gastric ulceration may develop secondary to the duodenal ulcer and may be the indication for operation.

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SYMPTOMS

Obstructing duodenal ulcers do not always give the classic symptoms of obstruction with nausea and vomiting, upper abdominal distention, and absence of the passage of gas or stool or rectum. In my experience, the most frequent single symptom has been increased ulcer pain with poor response to medical control due to incomplete gastric emptying. Nausea, distention, and a feeling of constant fullness or bloating are almost always a part of the symptom complex, but the ulcer pain may well overshadow these symptoms. Patients whose ulcers, in the past, have always been amenable to medical control with the use of bland foods or antacids now find that these foods or antacids no longer bring relief. With increasing pyloric stenosis, a pool of gastric juice and food remains in the antrum with continuing antral stimulation, antral distention, and stimulation to the secretion of more acid.

With persistent gastric stasis and antral stimulation, the increased amounts of acid secreted frequently cause further irritation of the duodenum with active ulceration and edema on top of the previous pyloric scarring, further increasing the obstruction. In some patients, a new gastric ulcer may occur. The patient frequently induces vomiting to gain relief from the feeling of fullness and pain. On admission to the hospital, after passage of a nasogastric tube and decompression of the stomach, striking relief of the pain may be achieved. Within 1 or 2 days of decompression of the stomach, gastric distention is usually relieved and gastric tone returns.

Figures 1 through 5 represent upper gastrointestinal roentgenographic series. Figure 1. Oblique view above shows pyloric stenosis and no visualization of descending duodenum.

DIAGNOSTIC STUDIES

Roentgenographic studies are extremely helpful in identifying the presence and site of gastric outlet obstruction or the incomplete gastric emptying. Lateral or oblique views of the pyloric channel and duodenum are essential to visualize this area and to determine the degree of pyloric stenosis (Figs. 1 and 2). In the absence of lateral or oblique views, on the standard anterior-posterior views the distended antrum often hides the pyloric region and duodenal bulb (Fig. 3). The stomach is dilated, frequently twice its normal size, gastric rugal folds are hypertrophied and thickened, and delayed gastric emptying is noted for a period of 6 or 8 hours following ingestion of a barium meal (Fig. 4). In some patients, as noted above, a gastric ulcer may be seen (Fig. 5). Gastroscopic examination will confirm the marked scanning of the pyloric channel. Usually the gastroscope cannot be passed out of the stomach into the duodenum. Retained food or secretions may be seen in the stomach, and the gastric mucosa is frequently hypertrophied and edematous.

Figure 2. Oblique view shows postbulbar narrowing and stenosis with an active postbulbar ulcer crater.

Figure 3. Anteroposterior view shows a dilated stomach with thickened gastric folds. The dilated antrum hides the area of stenosis.

Figure 4. This view shows a dilated stomach with thickened gastric rugal folds, and delayed gastric emptying.

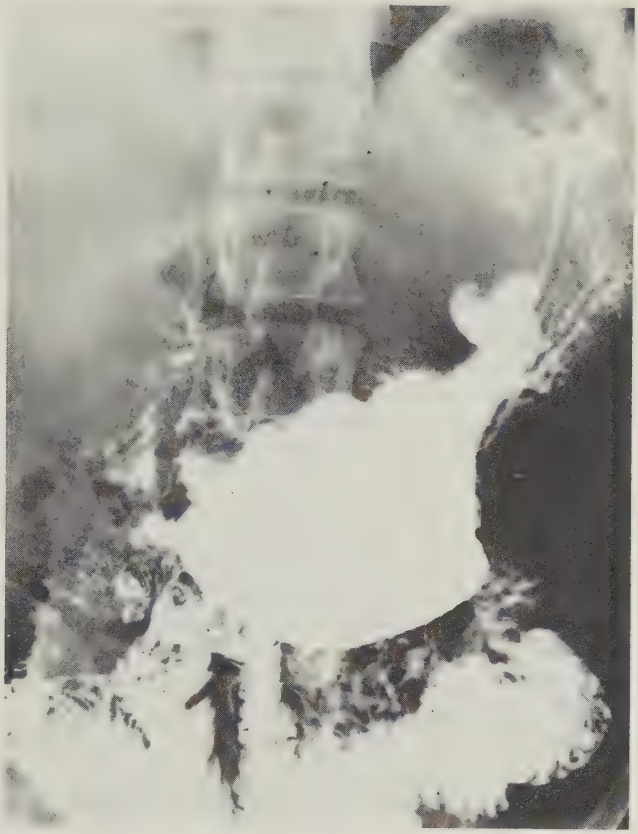

Figure 5. View of a lesser curvature gastric ulcer in a patient with duodenal deformity and persistent gastric stasis.

CLINICAL MATERIAL

In a personal series of 309 patients operated upon for duodenal ulcer disease between 1962 and 1975, approximately 83 patients (27 per cent) had evidence of an obstructing duodenal ulcer as the principal indication for surgery (Table 1). In this group of patients, duodenal ulcer disease was present symptomatically from 48 months to 45 years, with a mean duration of symptoms of approximately 11 years. All patients had medical treatment intermittently or sporadically for the relief of symptoms through the years. The symptoms of pyloric channel or gastric outlet obstruction had been present from 1 to 6 months prior to operation. Six patients had a previous episode of gastric obstruction, relieved by nasogastric suction and intensive medical therapy. Twenty-two patients had a history of bleeding, although none of the patients had had a serious or massive hemorrhage. Two patients had a previously perforated duodenal ulcer; both had had a plication procedure.

The operations performed in this group of patients are listed in

Table 1. *Indications for Surgery in Patients with Duodenal Ulcer, 1962–1975*

	NO. OF PATIENTS	PER CENT
Intractability	158	51
Obstruction	83	27
Bleeding	49	16
Perforation	19	6
TOTAL	309	100

Table 2; they include vagotomy and pyloroplastomy, vagotomy and gastrojejunostomy, vagotomy and gastroduodenostomy, vagotomy and antrectomy, and subtotal gastrectomy. The operations were elective in all patients; no operative mortality was recorded.

RESULTS

The results of operation were graded during follow-up evaluation by mailed questionnaires and by personal interviews from A through D, using the classification designed by Hoerr.[7] Patients graded A or B are considered excellent or good results; patients graded C are poor results, and patients graded D have symptoms of recurrent ulcer. The criteria for grading are:

A. No gastrointestinal symptoms.
B. Minor gastrointestinal symptoms; no evidence of a recurrent ulcer. The patient is satisfied with the results and is pursuing his usual occupation.
C. The patient is dissatisfied with the function of his gastrointestinal tract, but there is no evidence of a recurrent ulcer.
D. A proved or probable ulcer has recurred, or the patient is disabled from other gastrointestinal symptoms.

Of the 83 patients with obstructing duodenal ulcers, a group of 57 patients has now been followed from 2 to 13 years with a mean duration of follow-up 7 years; 53 per cent are considered an A result, 42 per cent are considered a B result, none are considered a C result, and 5 per cent (3 patients) are considered a D result, all because of recurrent ulcer

Table 2. *Operations for Obstructing Duodenal Ulcer, 1962–1975*

OPERATION	NO. OF PATIENTS	PER CENT
Vagotomy and pyloroplasty	62	75
Vagotomy and gastrojejunostomy	12	14.5
Vagotomy and gastroduodenostomy	5	6
Vagotomy and antral resection	3	3.5
Subtotal gastrectomy (without vagotomy)	1	1
TOTAL	83	100

symptoms. In two of the three patients, medical treatment alleviated all symptoms. Only one patient (2 per cent) required another operation, a subtotal gastric resection. None of the patients has had disabling gastrointestinal symptoms such as severe diarrhea, dumping, or postprandial distress.

DISCUSSION

Patients with obstructing duodenal ulcers usually have a long history of ulcer disease, an average of 11 years in our experience. During these years of the disease, medical control of ulcer symptoms has generally been effective, at least effective enough that surgery has never been advised or, if advised, the patient has decided not to have an operation. Thus, medical symptoms have not been incapacitating, and most patients have lived quite well with their symptoms until the complication of pyloric stenosis or gastric outlet obstruction developed.

It would appear, with mild pain or other symptoms of duodenal ulcer disease, that when surgical intervention becomes necessary because of the development of obstructive symptoms, the surgical procedure might be a conservative one, one that would relieve the obstruction as well as decrease gastric acidity. In addition the operation should be safe, since in almost all patients with obstructing duodenal ulcer the operation can be elective. I favor vagotomy and a drainage procedure for most patients with obstructing duodenal ulcer because it is the safest effective ulcer operation. Vagotomy and antrectomy is selected for young patients with severe ulcer symptoms or a history of multiple complications of the disease.

In the past, there was controversy as to whether a vagotomy should be performed for patients with obstructing duodenal ulcers. Bergin and Jordan,[1] and Kraft, Fry, and DeWeese,[9] in the late 1950s and early 1960s, cautioned against the use of vagotomy on the chronically obstructed stomach, reporting an increased incidence of postvagotomy gastric atony in these patients.

Other surgeons, including myself, have not found postvagotomy gastric atony to be a problem in patients with obstruction. In fact, many surgeons have found their best results with vagotomy and drainage for chronic duodenal ulcer disease in patients with gastric obstruction as an indication for the operation. Hoerr and Ward,[7] reviewing a 17-year experience with three operations for duodenal ulcer, all of which included truncal vagotomy (vagotomy-gastrojejunostomy, vagotomy-hemigastrectomy and vagotomy-pyloroplasty) found that all three operations when utilized for obstruction gave excellent results with low incidences of recurrent ulceration. Second operative procedures for recurrent ulcer were necessary in less than 4 per cent of patients regardless of the operative procedure performed. Vagotomy and gastrojejunostomy appeared to have the best results when utilized for patients with obstructing duodenal ulcers. Similar excellent or good results have been obtained by Davis and Williams[2] with vagotomy and pyloroplasty; by Ellis, Starer, Venables, and Ware[5] using vagotomy and gastrojejunostomy; and by

DeMatteis and Hermann[3] who combined vagotomy with a comparison of four types of drainage procedures.

An important aspect of the surgical management of obstructing duodenal ulcer is to obtain adequate drainage of the stomach, along with the vagotomy, at the time of the operative procedure. In my opinion, this can best be achieved by a Finney pyloroplasty or by an adequate gastrojejunostomy. A gastroduodenostomy (Jaboulay procedure) may provide excellent decompression of the chronically obstructed stomach, but a Heineke-Mikulicz pyloroplasty, in my opinion, is usually not as effective because the duodenal bulb or pyloric channel is too scarred. Vagotomy and antrectomy or hemigastrectomy, although an extemely effective ulcer operation, has a higher operative mortality (2 to 3 per cent), a greater incidence of postoperative dumping and diarrhea, and may not be necessary for any but a few patients with obstructing ulcers.[6, 11] Because of the degree of scarring in the pyloric channel in most patients with obstructing ulcers, I doubt that proximal gastric vagotomy and dilatation of the pylorus would be advisable.

Because of the safety of the procedure and its effectiveness in 95 per cent of patients, I continue to prefer vagotomy and Finney pyloroplasty or vagotomy and gastrojejunostomy for most patients with obstructing duodenal ulcers. In a young patient with a history of multiple complications of duodenal ulcer, now with symptoms of gastric outlet obstruction, I would choose vagotomy and antrectomy as the most effective ulcer operation, one which might be necessary in selected patients with a history of muliple ulcer problems.

SUMMARY

The incidence, pathogenesis, symptoms, roentgenographic, and endoscopic findings of patients with gastric outlet obstruction from a chronic duodenal ulcer have been reviewed. In the experience of many surgeons, including myself, vagotomy and an adequate drainage procedure (Finney pyloroplasty, gastrojejunostomy, or gastroduodenostomy) provide excellent decompression of the obstructed stomach, as well as excellent control of the ulcer disease in most patients. Postvagotomy gastric atony has not been a problem.

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Postoperative Gastric Retention and Delayed Gastric Emptying

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Since the beginning of the era of gastric operations, surgeons have been aware of the complication of delay in emptying of the stomach. There is no absolute criterion of diagnosis of delayed gastric emptying but we suggest the arbitrary definition of failure to establish adequate emptying of fluids through the pylorus or stoma by the fifth postoperative day. Some surgeons routinely continue nasogastric suction and do not allow oral feeding until the fifth postoperative day.[15] Others use no nasogastric suction and allow patients to eat and drink as soon as they are hungry and thirsty.[7] However, all surgeons recognize the phenomenon of the patient who, after a gastric operation, either vomits or has gastric aspirate volume in excess of intake at 7, 10, or more days after operation.

The incidence of the complication varies in reported series. Some claim never to encounter it,[7] others report incidences that vary with the operation and the type of patient operated upon. Bergin and Jordan[4] found delaying gastric emptying in 28 per cent of their patients treated by truncal vagotomy and pyloroplasty for duodenal ulcer with stenosis. Roth and his colleagues[12] reported that 27.5 per cent of their patients had gastric stasis after vagotomy and hemigastrectomy. In the early years of our experience with vagotomy and pyloroplasty we had delayed gastric emptying in 17 per cent of our patients but, as the result of a modification of technique described later, within 4 years the incidence has fallen to 2 per cent.[3]

CAUSES

The causes of delayed gastric emptying are (1) occlusion of the lumen at the stoma and (2) gastric atony as a result of vagal denervation

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of the motor fibers of the stomach. In those patients who have had an intestinal suture line and vagal denervation, both factors can occur. Predisposing factors include long-standing obstruction, inanition, gastritis, and chronic electrolyte depletion. There is no evidence that early drinking or eating predisposes to delayed emptying.

Luminal Obstruction

Temporary mechanical obstruction may result from stomal edema when too generous a cuff is inverted in a two-layer anastomosis. However, we believe that the commonest cause of serious prolonged delay in gastric emptying is minor suture line leakage resulting in an abscess with surrounding edema and sometimes fibrosis. Rarely stomal obstruction may result from kinking of a gastrojejunal anastomosis or from the technical error of suturing the front to the back wall of the anastomosis.

Obstruction of the stoma due to internal herniation or retrograde jejunogastric intussusception are well recognized but rare complications. A less well recognized but probably commoner cause is postischemic fibrosis of the duodenum following devascularization by a too thorough dissection before gastroduodenal anastomosis.

Vagal Denervation

Vagotomy divides both secretory and motor nerves to the stomach. It has long been known that truncal vagotomy alone, without a drainage procedure, is associated with a high incidence of gastric retention. Tanner[14] found that 49 per cent of patients had postoperative gastric stasis with vomiting and eructations after truncal vagotomy alone without drainage. However, even after this operation Dragstedt and his colleagues[5] found that if the stomach was emptied frequently by nasogastric suction, its tone gradually returned and after some weeks or months the patient was able to empty the stomach satisfactorily via the pylorus despite continued complete vagal denervation.

In the dog it has been shown that vagotomy temporarily disorganizes the electrical activity of the stomach and causes a permanent slowing of pacesetter potential in the corpus and antrum. Furthermore, there is permanent impairment of the electrical response to stimuli.[10] Studies of gastroduodenal motor co-ordination, also in the dog, have shown no long-term effect of vagal denervation either of the whole or of the proximal part of the stomach.[1]

Operations that retain the vagal innervation of the antrum (proximal gastric vagotomy) cause little disturbance of normal motor function. Studies of myoelectrical and motor activity of the stomach in man have shown that in the early postoperative days there is a decrease to 75 per cent of preoperative activity following proximal gastric vagotomy compared with a decrease to 38 per cent after selective and 31 per cent after truncal vagotomy.[13] In our experience it is possible, after proximal gastric vagotomy, to allow patients to eat and drink as soon as they wish without risk of complication. Johnston[9] has reported a cumulative review of over 5000 patients after proximal gastric vagotomy with a very low incidence of gastric retention.

DIAGNOSIS

In the immediate postoperative period, delay in gastric emptying must be distinguished from a generalized paralytic ileus and from mechanical intestinal obstruction. Although this will often be possible on clinical evidence, specialized investigation may also be required.

X-ray examination is helpful in that it gives a visual indication of the nature and site of any obstruction and an estimation of the volume of fluid passing from the stomach into the distal bowel. Although water-soluble contrast media such as Gastrografin are safer than barium if there is any question of leakage from the gut, they have the disadvantage of giving a less clear image and of being hyperosmolar. We recommend the use of a dilute barium suspension if the clinical findings exclude the possibility of leakage.

Gastroscopy will indicate whether there is mechanical obstruction to the stoma but in a patient with an anastomosis it may not be safe to distend the stomach with air in the first 10 days after operation. Endoscopy is, however, helpful in assessing patients with persistent delay in gastric emptying and may help to avoid reoperating on patients who have a widely patent stoma. Reoperation is a poor means of determining the cause of postoperative gastric retention.

There is a group of patients who have impaired gastric emptying which is not an obvious problem in the immediate postoperative period. They present at varying time intervals within the first year after surgery with symptoms of postcibal fullness, foul eructations, and vomiting of old food residues. There is usually a gastric outlet obstruction with or without the added effects of vagal denervation. The delay in clinical presentation is probably due to progressive fibrosis following the initial suture line leak and surrounding inflammation. Diagnosis in these patients is confirmed by barium meal examination. Where the clinical presentation is less florid and barium studies are equivocal, external scanning measurement of the gastric emptying of a radio-isotopically labelled solid meal is helpful.

PREVENTION

Prevention of the complication of suture line obstruction demands a meticulous operative technique. A two-layer intestinal closure causes more suture line inversion than does a single layer. However, a single layer anastomosis may have a greater tendency to leak, particularly if an interrupted suture "cuts through" inflamed or edematous tissue. When we began to employ vagotomy and pyloroplasty in the treatment of duodenal ulcer we followed the Heineke-Mickulicz technique with a two-layer closure. However, the high incidence of postoperative gastric retention (17 per cent in the first year) led us to adopt the Weinberg one-layer closure with interrupted silk. The results rapidly improved until the incidence of retention was 2 per cent. Later, two patients had prolonged gastric retention due to a peristomal abscess complicating leakage. As a consequence of these experiences, we now perform a

pyloroplasty with an inner layer of continuous chromic catgut that approximates the gastric mucosa to the full thickness of the duodenal wall. This is covered by an interrupted layer of silk sutures that suture the stomach wall to the duodenal wall with minimal inversion. This technique gives so little trouble that we no longer use postoperative nasogastric intubation and allow patients to drink as soon as they wish after the operation.

Preoperative cleansing of the stomach and removal of gastric residue is important in those patients with preoperative gastric outlet obstruction and those with gastric carcinoma. The normal stomach contains relatively few pathogenic organisms, but the obstructed stomach or a stomach with malignancy is heavily contaminated and is likely to be associated with a greater risk of local sepsis after operation. In these patients we employ preoperative gastric lavage and use preoperative parenteral antibiotic therapy, depending on the type of organism cultured from material obtained from the stomach at endoscopy or preoperative lavage.

Electrolyte repletion is important in patients with long-standing gastric outlet obstruction and vomiting. Intravenous sodium and potassium are given, but we do not find it necessary to take more than 24 hours in preoperative correction of electrolyte depletion. We have investigated the value of prolonged preoperative parenteral feeding in patients with gastric outlet obstruction who were undernourished but we could demonstrate no advantage of this often troublesome regimen when compared with the policy of rapid electrolyte repletion, early operation and early return to normal alimentation. We have found no advantage in prolonged nasogastric decompression of a preoperatively obstructed stomach. Gastric tone appears to return to normal within 24 hours after gastric retention is relieved.

There are no preventive measures that can be taken when performing total vagal denervation. However, when performing a proximal gastric vagotomy it is vital to ensure that the nerve of Latarjet is preserved. This is best achieved by dissecting the anterior and posterior leaves of the lesser omentum separately on the anterior and posterior aspects of the lesser curve, as far as possible away from the left gastric artery and vein. Hematomata must be avoided by gentle meticulous dissection with separate ligation of the many fine vessels. Some surgeons employ electrical nerve stimulation tests to demonstrate the integrity of antral innervation after proximal gastric vagotomy. We began by using this technique and can confirm that antral contraction can be checked visually and manometrically during operation. However, we find that with a careful technique the nerves were never damaged and in our practice routine nerve stimulation has been abandoned.

TREATMENT OF ESTABLISHED DELAY

When the diagnosis of delayed gastric emptying in the early postoperative phase has been established by the methods described above,

gastric decompression is advisable until normal gastric emptying is shown to have returned. When the obstruction is at the gastric outlet, the volume of fluid secreted into the stomach rarely exceeds 1 liter in 24 hours. If the delay is due to gastric atony, some emptying usually occurs and the volume of aspirate is less. Continuous gastric aspiration is therefore unnecessary, intermittently hourly aspiration is adequate, allowing the tube to drain freely into a drainage bag so that swallowed air may escape. Fluid and electrolyte replacement must continue and intravenous feeding with calories begun.

Drug Therapy

Urecholine has been shown to improve the rate of gastric emptying in patients with atony immediately after vagotomy when there is no mechanical obstruction, but to be ineffective if there is an element of obstruction.[6, 11] Similar claims have been made for the drug bethanecol chloride but so far the claims have not been fully substantiated. Metaclopramide (Maxolon) increases gastric emptying in the normal vagally innervated stomach.[8] There is no evidence of its efficacy in improving the rate of emptying of the stomach in the early phase of atony after vagal denervation. However, metaclorpromide may be of some value in patients with inadequate gastric emptying many weeks or months after operation.

Anti-inflammatory drugs have been recommended in patients with stomal edema; Butazolodin and steroids have had their advocates but they are dangerous drugs whose efficacy is unproven. We do not recommend their use. If tissue infection is playing a part in inflammatory edema then an antibiotic capable of achieving a high tissue concentration may be helpful.

Diet

When obstruction is complete due to inflammatory swelling there is no value in giving either liquid or solid food. However, fluids may be given by mouth and reaspirated to improve the patient's comfort and morale. It is important to remember that if clear water is given it returns as an isotonic aspirate and so electrolytes are dialyzed from the stomach.

When there is no mechanical outlet obstruction but the delayed emptying is due to vagal denervation there is evidence and clinical experience suggesting that solid foods are emptied better than liquids. A patient who continues to have large gastric aspirates when given a liquid diet may therefore empty the stomach relatively normally if given light solid food.

Reoperation

When a patient has established delayed postoperative gastric emptying, aspiration and parenteral feeding are continued in the expectation of return of normal emptying within 10 to 14 days. Fortunately, most patients fulfill this expectation. However, when complete gastric retention has persisted for 14 days after the operation the question of reoperation

has to be considered. It is important to attempt to diagnose the cause of the obstruction; by the 14th day endoscopy is safe and usually informative. If there is not complete stomal obstruction, we have continued a gastric aspiration regimen for up to 23 days in two patients who have subsequently recovered normal gastric emptying.[2] Follow-up studies 5 years later show that both patients have no symptoms related to any defect of gastric emptying. If, however, at 14 days there is still complete stomal obstruction, the fortitude of the patient and the medical attendants is usually weakening and reoperation has to be considered.

In those patients presenting some time after operation, drug therapy, as mentioned previously, may be of benefit if the major problem is atony; if the delay is due to stomal obstruction, however, reoperation will probably be necessary.

Choice of Operation

When the operation is at a gastroduodenostomy or pyloroplasty, it is usual to bypass the duodenum. We have experience of three patients treated in this manner, one of whom still failed to drain satisfactorily with a gastrojejunostomy and later required a Roux-en-y operation.

As an alternative approach, the stoma can be explored by a finger through a gastrotomy. If there is patency of the stoma or it can be established by gentle dilatation, then a tube can be passed through the stoma into the duodenum via the gastrotomy; another tube is passed into the stomach. The patient can then be managed by gastric aspiration and replacement into the duodenum either of the gastric aspirate or a prepared diet. Our experience is limited to three patients treated by this method, two fared well and normal emptying returned, the third later required a gastrojejunostomy. As a consequence of this limited experience, we cannot give an authoritative statement. However, we advise that if there is gross peristomal edema and patency cannot be established easily, gastrojejunostomy is advocated but, where technically feasible, we prefer the double intubation technique. We consider it unwise in the early stage or weeks after the first operation to take down the entire anastomosis, as this is invariably technically difficult and hazardous. In the rare cases where technical disasters have made further dissection inevitable, we advocate completing the operation as a truncal vagotomy and antrectomy with a Roux-en-y anastomosis and a protecting gastrostomy and duodenostomy (see below).

Anticipation

As previously stated we find that postoperative gastric retention is a rare complication in the patient with simple peptic ulceration requiring operative treatment. However, there are exceptional cases when the complication is expected, for example in patients with gross duodenal ulceration in whom there are special indications to perform a vagotomy and pyloroplasty or vagotomy, antrectomy, and gastroduodenal anastomosis. In such patients we feel that the discomfort and danger of prolonged nasogastric intubation is better avoided by performing a balloon catheter gastrostomy at the time of the first operation. Balloon

catheters have been developed with a third long limb that can be passed through the stoma into the bowel beyond. This allows simultaneous gastric decompression and duodenal feeding. There is much to recommend the use of this tube, although the fine distal tube can be difficult to site and the tubes may not readily be available. In 25 patients having total gastrectomy or Roux-en-y anastomoses, we have employed balloon catheter gastrostomy combined with a small balloon catheter duodenostomy in the second part of the duodenum. There were no local complications, so we were encouraged to use this technique after vagotomy and antrectomy. This combination has been trouble-free in eight patients and gave us complete command of the situation. We were able to aspirate or introduce fluid on either side of the anastomosis. By this technique prolonged delays in postoperative gastric emptying could be managed with ease for the surgeon and comfort for the patient.

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Assessment of Completeness of Vagotomy

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The objectives of truncal and selective vagotomies are complete interruption of the vagal nerve supply to the stomach; the objective of proximal gastric vagotomy is complete denervation of the parietal cell mass. Unfortunately, it is not possible, with the present tests, to prove that these objectives are met.

Tests to assess the "completeness" of vagotomy are both intraoperative and postoperative. Theoretically, intraoperative tests are preferred since an "incomplete vagotomy" could be detected during the operation. Postoperative tests that show an incomplete vagotomy would require another operation to complete the vagotomy. From a practical standpoint, intraoperative tests have several limitations and an incomplete vagotomy does not mean that the patient will suffer from persisting or recurrent duodenal ulcer. All these tests are designed to assess the anatomic and functional completeness of vagotomy and not to predict the risk of recurrent ulcer. Criteria of recurrent ulcer may be obtained by comparing the results of different tests with the clinical course of the patients, but valid criteria of complete vagotomy may probably be approached only by comparing the tests with findings during autopsy, and even then it is difficult to detect a primarily incomplete vagotomy because of possible nerve regeneration. Furthermore, apparently intact nerves may not function during the test, because of neuropraxia.

Objectives

This article reviews and assesses the tests for functional and anatomic completeness as well as prognostic value of vagotomy. Tests which are of major importance to the general surgeon are emphasized.

INTRAOPERATIVE TESTS

There are five intraoperative tests available to test completeness of vagotomy. These are (1) the electrical stimulation test; (2) leucomethy-

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lene blue test; (3) gastric pH-metry; (4) Congo and neutral red test; and (5) gastric adaptation.

Electrical Stimulation Test

Burge and Vane[14] described this test in 1958. The principle of the test is placement of a tube around the lower esophagus and vagal trunks for traction. Then a cuffed rubber tube is passed orally until its tip lies in the stomach. The electrodes, consisting of semicircular bands, are applied to the esophagus and the cuff is inflated. The pylorus is occluded with a clamp and the stomach filled with water; 40–50 volts per sec is used for stimulation and the intragastric pressure is recorded by a transducer. After a control stimulation all the vagus nerves that can be found are cut. The electrodes are then replaced and the stimulation is repeated; this procedure is followed until there is no increase in pressure (less than 2 mm of water).

The test was first used to ensure a complete truncal vagotomy and later it was applied to selective vagotomy.[13] Seven hundred patients underwent surgery and this was used in all. Ten patients were readmitted with recurrent ulcer in spite of a negative intraoperative test. Further follow-up data were not published. The use of the stimulation test has not reduced the frequency of positive insulin tests, [25, 52, 84] and one study[117] demonstrated no correlation between the stimulation and insulin tests. Another study[19] showed no difference in the incidence of recurrent ulcer when the electrical stimulation test was or was not used.

The test has several pitfalls: drugs given before the test may block vagal transmission, the electrodes may not encircle all the vagal branches, and the time of operation is prolonged. Randomized studies demonstrating the clinical value of electrical stimulation have not been performed and the conflicting data limit its routine use.

Leucomethylene Blue Test

In 1969, Lee[82] described a neural stain, leucomethylene blue, which stained small nerve fibres in 34 of 41 specimens. This yellow dye turns blue. According to Lee, small nerve fibers oxidize the dye more readily than other tissues. After dissection of the cardiac peritoneum and division of the main trunks the stain is applied to the surface of the esophagus. All tissues turn blue, but the excess stain is removed with saline solution. When used in rabbits, 25 of 26 darkly stained fibers from the esophagus contained nerves, but none of 14 pale blue stained structures.[50]

Clinical experience has not been as promising. Two studies[24, 35] revealed nerve tissue in no more than one third of the stained fibers. In another study staining of the esophagus where the surgeon had judged the vagotomy to be complete, demonstrated uncut nerves in 50 per cent of the patients.[55] The results of insulin tests in this group did not differ from those in another when the stain was not used. It must be concluded that leucomethylene blue is not a selective nerve stain, but may help complete a vagotomy by detecting small uncut vagal fibers. Further clinical trials seem warranted.

Gastric pH-metry

The Grassi test[43] is performed with a glass electrode through a gastrotomy. A pH probe is applied to the unstimulated gastric mucosa. Normal mucosal pH values vary between 5.5 and 7.0 during surgery. Acid zones after stimulation with histamine or pentagastrin are claimed to be due to vagal innervation. The vagal nerves can then be found and cut and the mucosa becomes neutral. Postoperative insulin tests are said to be negative if the pH test shows no decrease of pH after histamine.[44] Grassi has also reported intragastric pH values of 5.7 $\pm$ 0.7 during histamine tests 3 months after vagotomy in 106 patients with complete vagotomy according to pH-metry. Others[9] have questioned the reliability of the test; a pH of 5.5 or more during an augmented histamine test 3 months after any vagotomy is unusual, without pH-metry. Earlam[29] measured unstimulated gastric mucosal pH in 37 patients after vagotomy and found a mean value of 1.9.

The time of operation is prolonged by the test and the rate of recurrent ulceration has not been less. Further studies are needed to establish the value of the pH-metry test.

Congo and Neutral Red Test

Kusakari et al.[79] used a gastroscope through which Congo red was sprayed to the gastric mucosa. He determined it took less than one minute for the dye to change color because of an acid pH. The time required for complete color change was 8 to 20 minutes. The time interval is prolonged significantly after vagotomy. Correlation between Congo red and insulin tests was found in five patients. An area of initial color change corresponded to the site of an incomplete vagotomy in three patients. The test requires an assistant; it may be valuable in detecting uncut vagal fibers, but it is not known whether the incidence of recurrent ulcer will be lowered.

A combination of 2-deoxy-D-glucose (2DG) and neutral red has been used to test the completeness of vagotomy, both intraoperatively and postoperatively.[21, 118] 2DG is a more potent vagal stimulator of acid secretion than insulin. The neutral red dye is secreted by the parietal cells in the presence of intact vagal innervation of the stomach.[86] At surgery the presence of dye in the stomach is determined by swabbing the mucosa through the incision used for pyloroplasty. Change in color of the aspirate is noted postoperatively. Thirty minutes of observation are allowed after injection of 2DG before the test is called positive. It has been suggested[90] to stimulate the vagal nerves by the Burge machine instead of using 2DG, but it seems unappealing to add the drawbacks of the Burge test to those of the neutral red.

Gastric Adaptation

Köster and Madsen[65] distended the stomach by introducing an inflated balloon through a pylorotomy. The intragastric pressure was measured after 50 ml increments of water had been injected into the balloon (1000 ml was maximal). Pressures were measured before and immediately after vagotomy in 20 patients. The increase in pressure

after vagotomy did not correlate with the result of the postoperative insulin test, and no definite statement could be made about the completeness of vagotomy with this test. A smaller increase of pressure in dogs was noted after a deliberately performed incomplete vagotomy than after complete vagotomy.[18] However, the rise in pressure was the same whether the nerves had been cut or only loosely encircled by untied ligatures. Thus, measurements of gastric adaptation seem very limited in assessing the completeness of vagotomy.

POSTOPERATIVE TESTS

Insulin Test

Hollander[51] introduced the insulin test after it was shown in dogs that hypoglycemia resulted in an increase of acid concentration (acidity) in aspirates from Pavlov pouches but not from Heidenhain pouches. Basal secretion is collected during four consecutive 15-minute periods, then insulin 0.2 I.U. per kg is given intravenously and aspiration continued for eight 15-minute periods. Acidity is measured in each sample by titration to pH 7.0. The test is positive when the acidity increases more than 20 mmol per L above the basal level in any 15 minutes following insulin, unless the basal acidity is zero, in which case an increase of 10 mmol per L is sufficient. A blood glucose value below 45 mg per 100 ml is necessary to ensure a positive response in all patients before vagotomy.[12]

The incidence of positive tests within the first two weeks after truncal and selective vagotomy varies from 15 to 40 per cent;[58, 72, 95] the variations after proximal gastric vagotomy are even more pronounced (3 to 54 per cent).[61, 64, 72] Insulin tests performed several months after vagotomy show an increase in rate of positive responses,[37, 61, 74] but the quantitative increase in acid response is small in most patients. A response similar to that before vagotomy is seen in 5 to 10 per cent of patients after truncal vagotomy[70] and is usually due to intact large vagal trunks. This has been verified only in patients with recurrent dyspepsia suspected of having recurrent ulcers.[34, 71] Revagotomy usually results in a significant reduction of the acid response. It is less certain whether a small acid response to insulin is due to incomplete vagotomy. Secretory nerves may reach the stomach within the esophageal wall or through the diaphragm. The former possibility may explain the higher acid response to insulin after proximal gastric vagotomy when the dissection has cleared only the lower 2 cm of the esophagus, compared to a lower response when 5 to 7 cm of the esophagus has been cleared.[42, 47, 57]

A gastrin release following release of epinephrine during the insulin hypoglycemia[105] may also contribute to the small acid response, which can be reduced by beta-adrenergic blockade.[77, 92]

The increased rate of positive Hollander responses after the first 3 months may be explained by intraoperative neuropraxia, postoperative nerve sprouting, or nerve regeneration across a gap.[69, 102]

The value of insulin tests to determine the completeness of vagotomy is debatable. However, recurrent duodenal ulcer after vagotomy is more common in patients with a positive Hollander response than in those with a negative response.[47, 72, 76] The specificity of the response is 80 per cent in the early postoperative period, but only 65 per cent when the test is performed several months later.[72] The corresponding figures for sensitivity are 45 and 70 per cent respectively. The discriminative ability is therefore low. Many authors have presented other arbitrary criteria of recurrence for a positive test,[5, 6, 31, 38, 95, 107, 113, 114] but none of these criteria have increased the specificity or diagnostic value. Less arbitrary criteria have been derived[72] by comparing the results of insulin tests and clinical results several years after vagotomy; the values are chosen so as to place the largest possible proportion of both recurrences and nonrecurrences correctly in relation to a critical level of acid secretion.[67] A small increase in the diagnostic value resulted and the predictive value increased by adding criteria[39] or raising the critical level, but these measures reduced the sensitivity. Another way of increasing the diagnostic accuracy is by limiting the diagnostic criteria to dyspeptic patients after vagotomy;[72] recurrence may then be predicted with an accuracy of 80 per cent without any change in specificity or sensitivity, but this accuracy rate is still less than that of endoscopy. The higher the acid response to insulin is, the more likely that recurrent ulcer is present. It is, therefore, preferable to quote the actual figures for the acid response instead of a positive or negative result.[32, 33, 116]

The standard insulin test is not without risk. Death from coronary occlusion has been reported.[70] The insulin infusion test[17, 41] produces less side effects, since the degree of hypoglycemia required for a similar acid response is less than that after a single injection. This modification of the test is recommended, but no patient with cardiac disease should be subjected to any insulin test. Tolbutamide, which stimulates the endogenous release of insulin, results in a smaller drop in blood glucose, but the value of Tolbutamide tests[108] in assessing the completeness of vagotomy or predicting recurrent duodenal ulcer has not been established.

In summary, insulin tests should be performed routinely in patients without cardiac disease to assess the technique of the trainee vagotomist: acid responses similar to those in unoperated patients should not occur in more than 5 to 10 per cent after truncal vagotomy and probably in a smaller number after selective and highly selective vagotomy. The test should also be performed in patients with recurrent ulcer after vagotomy; a reoperation should then include revagotomy if the acid response is similar to that in unoperated patients with intact vagal nerves.

2-Deoxy-D-Glucose Test

2-deoxy-D-glucose (2DG) is a more potent activator of gastric acid secretion than insulin;[30, 49] it inhibits cellular anaerobic glycolysis, and the vagal centers are stimulated by the resulting intracellular glucopenia.[112] The method of performing this test is similar to that of the

insulin test; the dose is 2-DG, 40–50 mg per kg body weight, and the calculated dose is injected intravenously.

2-DG produces an earlier and greater acid response than insulin in patients with incomplete vagotomy according to Hollander,[110] but it is not known whether 2-DG is superior to insulin in assessing the completeness of vagotomy or predicting the risk of recurrence. The side effects are similar to those seen during insulin tests and the test should not be performed in patients with cardiac diseases.

Basal Acid Secretion

Measurements of basal acid secretion before and after different vagotomies show reductions in output of 80 to 90 per cent.[45, 70] However, resection of uncut vagal trunks during revagotomy also reduces the basal output by an average of 80 to 90 per cent. The reproducibility of these measurements is low.[119] Basal and insulin activated acid secretion are significantly related in patients with duodenal ulcer.[4, 70] Arbitrary criteria of incomplete vagotomy based on basal secretion measurements have therefore been suggested,[4, 106] but the only thing which can be shown for certain is that recurrent ulcer is correlated, with rare exception, to basal acid secretion.[53, 70, 73, 76] The predictive value of recurrent ulcer by this method is low, whether the criteria are arbitrary or calculated by discriminative analysis. Accordingly, the value of basal acid secretion alone is of little clinical value.

Augmented Histamine Test

Kay[62] introduced this test in 1953 after it was shown that subcutaneous injection of histamine acid phosphate 0.04 mg per kg body weight produced a maximum acid response, which was reproducible. An antihistaminic should be given 30 minutes before the test, to protect the patient against systemic side effects. Gastric secretion is aspirated during four 15-minute periods before (BAO) and after histamine (MAO). Augmented histamine response (AHR) is the output from 15 to 45 minutes after histamine, multiplied by two. PAO is the sum of the two highest consecutive 15 minute outputs, multiplied by two. AHR and PAO are nearly identical. The difficulty of interpreting PAO may be avoided by continuous intravenous infusion of histamine.[81] A highly significant correlation exists between acid output after subcutaneous injection and intravenous infusion, but the latter is 20 per cent higher. MAO is significantly related both to BAO and the number of parietal cells in the intact stomach.[16, 85]

The maximum acid secretion is reduced an average of 60 to 70 per cent after vagotomy.[6, 7] Drainage alone does not reduce the acid output.[36] The reduction seems to be permanent, whether or not the Hollander response to insulin is positive.[8] Maximum secretion may be restored to some degree by increasing the dose of histamine;[2] this indicates a decreased sensitivity of the parietal cells to histamine after vagotomy.

The per cent reduction of PAO is less in patients with positive Hollander tests than in those with negative tests;[95] it is also less in patients with positive Hollander responses within 0 to 45 minutes than in

those with later positive responses.[68, 95] The vagotomy may therefore be more complete in the latter group. What may be more important, is PAO before and after vagotomy.[46] The response to insulin after vagotomy seems to be a better test of estimating postvagotomy-PAO than preoperative PAO, i.e., the completeness of vagotomy is more important for the resulting maximum acid secretion than the number of parietal cells.[46] Accordingly, the per cent reduction of AHR after vagotomy is less in patients with apparently intact vagal trunks (as found during revagotomy) than the average reduction of 60 to 70 per cent.[70] The comparison of preoperative and postoperative histamine tests supplies the same information about the completeness of vagotomy as a postoperative insulin test alone, and no more.

The risk of recurrent ulcer after vagotomy is related to maximum acid secretion, both before and after vagotomy.[72, 83, 93] In a series of 500 patients with duodenal ulcer,[72] men with a preoperative PAO of more than 46 mmol per hour had a risk of recurrence amounting to 21 per cent within 6 to 8 years after truncal vagotomy. The critical level in women was 41 mmol per hr, and the recurrence rate was 28 per cent above this level. Below the levels, the risk was 5 per cent and 1 per cent. In a smaller series of 117 men treated with selective vagotomy and pyloroplasty the figures were similar.[76]

The critical level of PAO 10 days after vagotomy is about 20 mmol per hr in men and 18 mmol per hr in women. The risk of recurrent ulceration is approximately 25 per cent above and 5 per cent below the levels.[72] The per cent reduction of PAO also has a discrimination ability,[27, 72] the critical level being about 65 per cent. Patients with high PAO values before vagotomy are less likely to have a postoperative PAO below a safe threshold and therefore have a higher risk of recurrence. However, this may not be true after proximal gastric vagotomy.[59]

A medical vagotomy[40] has been suggested to predict the reduction of PAO after surgical vagotomy. On one day the standard histamine test is performed; on the other the nerves are blocked by injection of hexamethonium and atropine before the test. The reductions of PAO after medical and later surgical vagotomy are significantly related, but the test frequently underestimates the surgical reduction,[100] and the prediction is so poor in one-third of the patients[63] that the test has no clinical value.

Criteria of recurrence based on augmented histamine tests are no better than those based on insulin tests. However, the surgeon's technique may be assessed and the need of revagotomy estimated by histamine tests. Because of the side effects, histamine should now be replaced by pentagastrin.

Maximal Histalog Test

Histalog (Betazol) is an analogue of histamine, which produces an acid response similar to that during intravenous infusion of histamine.[60, 121] An antihistamine is not required, but a 2-hour collection period after stimulation is necessary, since PAO often falls within the second hour.[115] Histalog also has side effects; therefore, this test should be replaced by pentagastrin.

Pentagastrin Stimulation Test

Pentagastrin (Peptavlon, I.C.I.) contains the active tetrapeptide of gastrin and is the stimulant of choice in tests of maximum acid secretion.[22] Only minimal and transient side effects have been noted. A subcutaneous injection of 6 μg per kg body weight produces an acid response nearly equal to that of histamine.[3, 87] The responses to intravenous infusions of maximal and supramaximal doses of histamine and pentagastrin are indistinguishable over 135 minutes.[1] The acid responses to both stimulants are reduced to the same degree after different vagotomies.[56, 91] The sensitivity of the parietal cells to pentagastrin as well as to histamine is decreased after truncal and selective vagotomy;[88] the dose of pentagastrin required to elicit maximum acid output after proximal gastric vagotomy seems to be the same as before vagotomy.[61]

Pentagastrin should replace histamine for use in gastric acid secretion tests.

pH Telemetering Capsule

A pH-sensitive endoradiosonde (Heidelberg capsule) may be used to assess gastric acid secretion.[89] The patient swallows an untethered pH-capsule and the basal pH is noted by a receiver which activates a pen recorder. Intragastric titration may then be performed by administration of a known amount of bicarbonate and the time taken for a return to basal pH recorded.

AHR is related to the "alkali test time" measured during augmented histamine tests,[23] and reasonable correlation has also been found between the results of pentagastrin and pH-telemetry tests.[103] No studies have been published on pH-telemetry with intragastric titration after vagotomy. pH measurements without titration have been compared with results of insulin tests after vagotomy, but no quantitative relationship has been established between completeness of vagotomy and pH measurements.[111] So far, radiotelemetry cannot be recommended for clinical use.

Pepsinogen and Pepsin

Pepsinogens are found in gastric and duodenal mucosa. They are separated into two groups, Pg I and II, and the concentrations in serum can now be determined by radioimmunoassay.[96] Measurements of Pg I during collection of basal acid secretion are positively correlated to PAO, both before and after vagotomy,[97, 98] but it is not known whether Pg I is of any help in assessing the completeness of vagotomy.

One study[98] has shown a higher mean concentration of Pg I in patients with recurrent ulcer after vagotomy than in those without recurrence. However, recurrences after vagotomy and pyloroplasty were compared to nonrecurrences after vagotomy and antrectomy, the latter having a reduced number of chief cells. Serum Pg I has also been measured during Histalog tests.[99] An increase was observed in 20 of 20 patients with recurrence after vagotomy and pyloroplasty, when compared to basal serum Pg I; a decrease was seen in 20 of 25 patients

without recurrence after vagotomy and antrectomy. However, the increase of serum Pg I after Histalog was related to a positive Hollander response to insulin, whether or not the patient had recurrence. It may therefore be related to an incomplete vagotomy. Further studies are needed to evaluate the clinical importance of this "tubeless" method of measuring gastric function.

Measurements of gastric secretion of pepsin or its fractions are not standardized. The basal secretion is probably decreased by vagotomy.[10, 26] Insulin hypoglycemia produces a quantitative and parallel response for both pepsin and acid in healthy men.[120] According to Hollander,[101] a response has also been reported in 20 per cent of patients with complete vagotomy; this could be due to an incomplete vagotomy, since a minor acid response could have been masked by buffers in the gastric contents.

The pepsin response to histamine and pentagastrin[94, 113] is approximately one-third of the acid response, both before and after vagotomy, and may possibly be used to predict the risk of recurrent ulcer. A single study has shown that the response to insulin is at least 70 per cent of that to pentagastrin in 95 of 100 patients with intact vagi;[113] only 12 per cent had a pepsin ratio above 0.70 after vagotomy, but a much higher proportion (59 per cent) was found in patients with suspected recurrent duodenal ulcer. However, a valid appraisal of the use of pepsin measurements in assessing the completeness of vagotomy and risk of recurrence cannot be made before more experience is available.

Gastrin After Vagotomy

Insulin hypoglycemia produces an increase in serum concentrations of gastrin as measured by radioimmunoassay in patients with intact vagi.[48, 104] The basal level of serum gastrin is generally elevated after vagotomy, regardless of the completeness according to Hollander.[15, 48, 104] The response to hypoglycemia has been reported to be abolished after complete vagotomy, but still present although reduced, after incomplete vagotomy, using the criteria of Hollander. However, "complete" proximal gastric vagotomy did not abolish the gastrin response.[66] Other groups have found hypoglycemia release of gastrin after "complete" vagotomies,[15, 104] but probably a smaller response than in patients with positive Hollander tests.[54]

It has not been established whether gastrin measurements are of help in assessing the completeness of vagotomy, and whether they have any prognostic value is in question,[20, 75] except in patients with the Zollinger-Ellison syndrome or retained antrum.

Gastric Myoelectrical and Motor Activity After Vagotomy

An omnipresent rhythm of electrical waves known as the pacesetter potential (PSP) is well established in the lower two-thirds of the stomach.[80] Regular antral myoelectrical activity, measured by nasogastric mucosal electrodes, is decreased after vagotomy;[109] the decrease is more pronounced after truncal and selective vagotomies than after proximal gastric vagotomy. The mean amplitude of PSP is also reduced by dif-

ferent vagotomies. The shape of PSP is changed from peaked to sinusoidal after truncal and selective, but not after proximal gastric vagotomy. The changes in amplitude and shape are permanent, while regular activity returns to preoperative levels after some time.[109] The frequency of motor waves is permanently reduced after all three vagotomies.

The extent of denervation of the antrum may be checked, since the electrical activity is disorganized for up to 3 weeks after truncal and selective vagotomy and the shape of PSP is changed for as long as 8 years, while proximal gastric vagotomy only results in a reduced amplitude.[28]

No difference has been found in PSP between patients with negative and late positive Hollander response,[109] but one patient with recurrent ulcer and early positive insulin test had an amplitude which was significantly greater than other patients. So far, recordings of PSP are not suitable for routine use in the clinic.

CONCLUSION

None of the intraoperative tests to assess the completeness of vagotomy seem to be reliable. Leucomethylene blue is certainly not a selective nerve stain, but it has revealed uncut small nerves in half the patients otherwise judged to have a complete vagotomy and may therefore be recommended for clinical use; it is inexpensive and adds little time to the operation.

I believe postoperative insulin tests assessing vagotomy should be performed routinely to assess the technique of the trainee vagotomist, but insulin tests per se may be replaced by preoperative and postoperative pentagastrin tests. An incomplete vagotomy is probably found in most patients with little reduction of maximum acid secretion or an acid response to insulin similar to that in unoperated patients. An insulin test should therefore also be performed in patients with recurrent duodenal ulcer after vagotomy to investigate the necessity of doing a revagotomy; a pentagastrin test may replace the insulin test if a measurement of maximum acid secretion has been done before the original vagotomy.

It is not important whether acid secretion measurements are performed one week or several months after vagotomy, since a small acid response, which may be concealed by gastric retention of food remnants in the early postoperative period, is of no clinical value.

Pentagastrin and insulin tests should not be performed to predict the risk of recurrent ulcer after vagotomy. Other clinical examinations with a higher diagnostic accuracy are available.

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Marginal Ulcer: A Guide to Management

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A marginal ulcer occurring after an initial operation for gastroduodenal ulcer disease is a serious threat to the patient and a difficult challenge to the surgeon. This review is intended to acquaint the surgeon with factors in the etiology of marginal ulceration, and to provide some useful diagnostic aids. Marginal ulcer is a complex problem, and a well-planned method of diagnosis and treatment is therefore essential.

Incidence

Marginal ulcers most often occur following operations for duodenal ulcer disease.[62, 69] It is estimated that a marginal ulcer will subsequently develop in 3 to 10 per cent of patients operated on for duodenal ulcer. It is distinctly more common in men than in women (6:1).[13, 17, 31, 69] The reported incidence of marginal ulcer varies depending on the initial operation for peptic ulcer disease. It ranges from more than 30 per cent after simple gastroenterostomy[36] to less than 1 per cent following vagotomy and resection[29] (Fig. 1). Of the current, popular operations, vagotomy and gastric resection consistently has the lowest reported ulcer recurrence rate.

Factors in the Development of Marginal Ulcer

Inadequate Surgical Procedures. The two most common causes of marginal ulcers are inadequate vagotomy and simple gastroenterostomy. An effective truncal vagotomy eliminates direct vagal stimulation of acid, decreases the release of gastrin, and reduces the response of the parietal cell to various stimuli. An inadequate vagotomy contributes to the genesis of a marginal ulcer by allowing the continued function of one or more of these factors. Simple gastroenterostomy reduces neither vagal stimulation nor antral gastrin release, nor does it reduce the parietal cell mass. Interestingly, and in contrast to other

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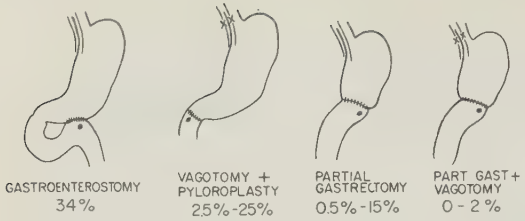

Figure 1. Marginal ulcer incidence rate.

operations for peptic ulcer disease, a period of 10 or more years may be required for marginal ulcer to develop following this procedure.

A third common surgical deficiency is an inadequate gastric resection. While resection of two-thirds or more of the stomach without vagotomy has a low rate of ulcer recurrence,[7] experience has shown that lesser resections have a higher rate of failure.[20]

Lastly, a retained distal antrum in the duodenal stump following a Billroth II gastric resection is highly ulcerogenic. Since it is not inhibited by gastric acid, the retained antrum elaborates excessive quantities of gastrin, constantly stimulating the gastric remnant to produce increasing quantities of acid. For this reason, a retained antrum may simulate the Zollinger-Ellison syndrome.[49, 50, 60] Resection of the retained antrum produces healing of the marginal ulcer.[60]

Unrecognized Endocrine Factors. There appears to be a strong relationship between hyperparathyroidism and ulcer disease. It is estimated that the prevalence of peptic ulcer disease in hyperparathyroid patients is ten times that of the general population.[4] Conversely, hyperparathyroidism is found in ulcer patients with ten times the frequency of that in the normal population. Further, the correction of hyperparathyroidism has been followed by healing of the ulcer in about one-half of the patients having both problems.

The Zollinger-Ellison Syndrome. The presence of a gastrin-secreting tumor (gastrinoma), although rare, is an important cause of recurrent ulcers. Most patients with gastrinomas are not diagnosed early and, therefore, are treated as having ordinary duodenal ulcer disease. Regretably, three-fourths of the gastrinoma patients have had a previous operation for ulcer disease and have experienced a recurrence of the ulcer.[15, 68] This is a significant factor in the high morbidity and mortality with this disease. Although gastrinomas have been found only rarely at operation for recurrent ulcers (1.8 per cent),[1, 23, 39, 57, 69] it is important that the marginal ulcer patient be thoroughly investigated for this condition preoperatively, because proper treatment of the Zollinger-Ellison syndrome is usually total gastrectomy.

Ulcerogenic Drugs. The ingestion of a number of drugs, including salicylates,[35, 40] indomethicin, phenylbutazone,[32, 44] corticosteroids,[41, 53] and reserpine[24, 55] have been associated with peptic ulcer. A careful history should be taken for the use of these agents and they should be discontinued during the evaluation of the patient with a marginal ulcer.

Aids in Evaluation

History. Marginal ulcer is one of the few causes of left upper quadrant abdominal pain. Such pain (or recurrent epigastric pain), especially if relieved by antacids, should strongly suggest a marginal ulcer in a patient who has previously been operated for ulcer disease. Pain is evident in two-thirds of patients within 2 years,[69] and is often accompanied by a significant weight loss occurring after the previous ulcer operation.[27, 37, 38] The stool should be carefully examined for occult blood which occurs in 20 to 33 per cent of cases.[3, 16] Patients who have had a previous ulcer operation and who complain of foul breath (pyrosis), the acute onset of feculent smelling emesis, or diarrhea containing undigested food particles, should be suspected of having a gastrojejunocolic fistula.[8]

Roentgenography. While an upper gastrointestinal series is usually done, in almost half the cases it may be both difficult to interpret and generally uninformative.[7, 11, 14, 69] Therefore, a "negative" upper gastrointestinal series does not exclude this entity. When available, a comparison with an earlier postoperative gastrointestinal barium study may be helpful in determining if a marginal ulcer is present.

Endoscopy. Our experience, as well as that of others, indicates the superiority of fiberoptic endoscopy over roentgenography in diagnosing a marginal ulcer. The presence of the ulcer should be documented by a photograph to avoid confusion with "suture abscesses" or stomal erosions. Healing of the ulcer can be followed by repeat endoscopies.

Acid Secretory Studies. Although acid secretory studies are infrequently helpful in diagnosing duodenal ulcer disease, they may be useful in evaluating patients with marginal ulcer. To be meaningful, the tests must be done accurately after the nasogastric tube has been inserted under fluoroscopic control. Measurement of the basal acid secretion may provide valuable information. Following either adequate vagotomy or gastric resection, basal acid secretion is reduced to 0.3 mEq per hr or less.[2] Marginal ulcer patients, however, frequently have a basal acid secretion of 2.0 mEq per hr or more,[50] and histamine-stimulated values of 6.0 mEq per hr are strongly correlated with the presence of a marginal ulcer.[18]

The Hollander Test (insulin hypoglycemic stimulus) has been widely used in the evaluation of patients with a marginal ulcer resulting from presumed "incomplete" vagotomy. Unfortunately, the test leaves much to be desired,[22] since criteria for interpretation are variable. The test is unpleasant and dangerous, and it is at best an imperfect indicator of vagal integrity. It should be emphasized that a "positive" Hollander test does not necessarily mean that the vagotomy is clinically inadequate, since many patients with "positive" Hollander tests show no evidence of marginal ulcer.[18, 46, 55] Similarly, patients with "negative" Hollander tests have been shown to have marginal ulcers.[2, 58] In our opinion the test should be abandoned.

Stimulated acid secretion is of particular value in the Zollinger-Ellison syndrome. Betazole (Histalog) is an excellent stimulus because of its safety, potency, rare side effects, and duration of action. The ratio

of the basal to maximal acid output (BAO/MAO) following betazole administration may be 0.6 or more in the Zollinger-Ellison syndrome. The acid and serum gastrin response to a calcium or secretin infusion may also be of help. Calcium is normally only a weak stimulus of acid secretion. In the presence of a gastrinoma, however, it may be as potent as betazole. It is a powerful stimulus for the elaboration of gastrin by the gastrinomas present in the Zollinger-Ellison syndrome. Secretin, given intravenously, also causes the the release of gastrin from gastrinomas, but inhibits the release of gastrin from the antrum in patients with duodenal ulcer disease.[25] Therefore, it is also of value in differentiating patients with gastrinomas from those with retained antrum.

Serum Gastrin. Just as the relationship between gastrin and peptic ulcer disease remains unclear, the role of gastrin in the development of marginal ulcers is still unknown. It may be pointed out, however, that this hormone may be more important in the development of marginal ulcer than in the genesis of ordinary peptic disease, at least in some patients who have had vagotomy without gastric or antral resection.[25, 61] At present, definitive serum levels of gastrin in marginal ulcer after the various ulcer operations for peptic ulcer disease remain undefined. However, serum gastrins should be obtained in all patients with marginal ulcer to exclude the diagnosis of gastrinomas. An elevated serum (absolute values depend on the laboratory performing the test) in the absence of a retained antrum is virtually diagnostic of a gastrin-producing tumor. Since in our experience 40 per cent of patients with gastrinoma have basal gastrin concentration in the normal range, stimulation with a calcium infusion or secretion injection should be done if the basal gastrin values are not elevated.

Serum Pepsinogen. A radioimmunoassay for serum pepsinogen Group I which is simple, sensitive and reliable has recently been developed.[47] The Group I pepsinogen level is an accurate reflection of the secretory capacity of the fundic mucosa (Samloff, personal correspondence). Experience indicates that the diagnosis of marginal ulcer may be aided by determination of the betazole-stimulated Group I pepsinogen level in patients suspected of having marginal ulcer.[48]

Calcium. Unrecognized hyperparathyroidism as a cause for marginal ulcer has been described.[1, 5, 69] Multiple serum calcium determinations should be done to detect this condition and if elevated, primary hyperparathyroidism should be strongly considered. If found, parathyroidectomy should be considered as it may cure the ulcer.

Radioisotope Scan. Retained gastric antrum after a Billroth II gastrectomy can be difficult to detect. A technetium pertechnetate radioisotope scan has been used to detect the retained antrum, and allows for its easy differentiation from gastrinoma.[10] Also, endoscopic examination of the afferent limb may show the retained segment.

The management of the marginal ulcer is based on recognizing and correcting the factor responsible for the recurrence. The factor(s) are often overlooked and may in fact be unknown. Therefore, in evaluating the patient with a postoperative recurrent ulcer, the investigation must

be complete. A format summarizing the steps in the evaluation of such a patient is given in Table 1.

Treatment and Results

NONSURGICAL TREATMENT. Less than a third of patients who have marginal ulcer and are treated with traditional medical management have had good results.[3, 5, 11, 16, 52, 59] Because of the consistently poor long-term results, medical (as opposed to surgical) approaches to marginal ulcers should be limited and reserved for cases which are very uncomplicated and mild, or for those in which the surgical risk is prohibitive. Gastric irradiation occasionally can provide adequate palliation. The use of metiamide or cimetidine may be efficacious but data are not yet available in this regard.

SURGICAL TREATMENT. Marginal ulcer almost always responds best to surgical treatment. The operation to be done depends on such considerations as the original surgical procedure, the condition of the patient, the extent and location of the ulceration involved, and the presence or absence of a specific ulcerogenic factor. A review analyzing the surgical results in over 3000 cases of marginal ulcer has recently been published.[54]

It should be emphasized that the cause of ulcer recurrence in most patients is a failure in diagnosis, technique, or judgment. Most patients will have some inadequacy of their initial operation as the cause of their recurrence rather than an occult factor.

Local excision of the ulcer, takedown, or establishment of a gastroenterostomy, fistula excision, or other non-acid reducing procedures should *not* be used. Only acid and pepsin reducing procedures such as vagotomy, resection, or the combination of the two should be employed in the treatment of marginal ulcer. Our experience has shown that regardless of the initial operation, combinations of vagotomy and gastric resection have a lower second recurrence rate than do the same procedures used alone.

In an individual patient, however, the initial procedure performed greatly influences the efficacy of each of the various re-operations for marginal ulcer. The most common initial procedures are discussed below.

Recurrent Ulcer Following Gastroenterostomy. Although combined vagotomy and antrectomy should theoretically be the procedure of choice, a review of the literature shows that marginal ulcer has been treated best by a 70 per cent gastric resection alone.[11, 41, 62, 69] Vagotomy alone, since it may be inadequate, should be reserved only for high risk patients, those who are not hypersecretors, and those with uncomplicated ulcers,[3, 11, 33, 51, 64, 66] or for those surgeons who have demonstrated a low incidence of inadequate vagotomy.

Marginal Ulcer Following Partial Gastrectomy. Depending upon the adequacy of the original resection, vagotomy alone may be an effective operation for marginal ulceration following partial gastrectomy. Vagotomy and a re-resection is indicated only if the original resection is inadequate or if the ulcer diathesis is virulent.[31, 42, 62]

Table 1. *Aids in Evaluation of Marginal Ulcer*

AID	RESULT	DIAGNOSIS	TREATMENT
1. Serum calcium levels	Persistent elevation (at least three occasions)	Hyperparathyroidism	Parathyroidectomy
2. Gastric acid secretion	a. BAO/MAO:* > 0.6	a. Zollinger-Ellison syndrome	Total gastrectomy
		b. Isolated retained antrum post-Billroth II (see #3,5,7)	Removal of antral remnant
	b. BAO: > 2.0 mEq	a. Incomplete vagotomy	Re-vagotomy
		b. Possible Zollinger-Ellison syndrome (see #3,4,5)	Total gastrectomy
3. Serum gastrin level	> 500 pg per ml†	a. Zollinger-Ellison syndrome	Total gastrectomy
		b. Isolated retained antrum post-Billroth II (See #5,7)	Removal of antral remnant
		c. Pyloric obstruction	Vagotomy, hemi-gastrectomy

4. Calcium infusion	Marked increase in gastric acid (300 per cent of BAO) and/or serum gastrin level (200 per cent of basal level)	Zollinger-Ellison syndrome	Total gastrectomy
5. Secretin infusion	a. Increase in gastric acid and/or increase in serum gastrin level	Zollinger-Ellison syndrome	Total gastrectomy
	b. Decrease in acid and serum gastrin	Isolated retained antrum post-Billroth II	Removal of antral remnant
6. Pepsinogen response to betazole HCl (Histalog)	Increase of 100 per cent over basal level	Incomplete vagotomy	Re-vagotomy
7. Technetium pertechnetate scan	RUQ uptake separate from fundus	Isolated retained antrum post Billroth II	Removal of antral remnant

*BAO: Basal acid output in mEq per hour; MAO: Maximal acid output in mEq per hour.

†The "normal" and "Zollinger-Ellison" range of serum gastrin levels vary from lab to lab. Serum gastrin levels in excess of 500 pg per ml are in the Zollinger-Ellison range in our lab.

Recurrent Ulcer Following Vagotomy and Drainage. An antrectomy and a re-vagotomy is probably the best treatment in this instance.[56, 59, 68] If, however, the patient is a high risk with an uncomplicated ulcer and one or more large residual vagal trunks are found, re-vagotomy alone may suffice.

Marginal Ulcer Following Vagotomy and Resection. Most marginal ulcers after this procedure have been due to an incomplete vagotomy or an inadequate resection, and can be rectified by correcting the appropriate deficiency.

Mortality and Morbidity

The overall mortality rate is approximately 4 per cent. Some 4 to 10 per cent of patients will have a second recurrence despite optimal management. In selected instances a total gastrectomy may be required to arrest the ulcer diathesis.

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Postoperative Alkaline Reflux Gastritis

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The reflux of bile, pancreatic, and intestinal secretions into the stomach is frequently observed when the pyloric sphincter is resected, bypassed, or incompetent. Although reflux may occur in normal persons, it occurs more frequently after gastric surgery.[45] These secretions may be "innocuous" in some patients,[16] but in others a clinical syndrome of varying severity may develop. This has been called reflux gastritis,[22] bile gastritis, alkaline gastritis,[24] or postoperative reflux gastritis.[56] The term bilious vomiting[3] has also been used but it is less accurate and descriptive of only one aspect of this syndrome.

The syndrome is characterized by epigastric pain, weight loss, nausea, vomiting of bile, and less frequently by iron deficiency anemia. Only recently have publications reviewed this syndrome,[3, 15, 22, 30, 56] but it was first described nearly 100 years ago. Bile vomiting following a gastroenterostomy was noted by Wolfler in 1881[59] and was again reported by Billroth in 1885 after a gastric resection.[8] This apparently long delay in recognition was due to several reasons. First, since nausea and vomiting occur frequently after gastric surgery, little attention may have been given to these symptoms. Second, many surgeons included the symptoms of reflux with other postgastrectomy sequelae. Only in the last 10 to 15 years has reflux gastritis been accurately differentiated from marginal ulcer, the dumping syndrome, and the afferent loop syndrome so that accurate treatment could be given.

This article reviews the incidence, etiology, diagnosis, and treatment of postoperative alkaline gastritis.

INCIDENCE

Large series of prospective endoscopic studies following gastric operations have not been done in asymptomatic patients. Therefore, there are no accurate data on the incidence of reflux. Palmer in 1954 noted that 50 per cent of patients who underwent gastric surgery had endoscopic evidence of reflux.[45] Benedict in 1959 noted changes in the gastric mucosa due to reflux in 45 of 50 patients after gastric opera-

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tions.[6] Since reflux may not be uncommon after surgery three clinical situations may exist: (1) normal endoscopic examination, (2) endoscopic and histologic demonstration of gastritis with the clinical syndrome, and (3) endoscopic and histologic demonstration of gastritis without clinical symptoms.

An estimated 5 to 35 per cent of postgastrectomy patients will have reflux gastritis or bile vomiting or both.[27]

ETIOLOGY

Experimental Studies

Bile, or pancreatic or intestinal secretions alone or in combination have been incriminated in the development of reflux gastritis.[7, 9, 11, 12, 17, 20, 22, 56] Much is based on experimental and clinical observations and controversy still exists as to which factor is most important.

Many ingenious experiments and animal models have been studied to reproduce the features of reflux gastritis. Most investigators have used histologic changes in the gastric mucosa as the sole criterion. The clinical applications of these experiments are therefore limited because (1) symptoms may not be produced despite the histologic changes, and (2) many experiments have not been combined with vagotomy or resection which is the usual setting for the development of reflux gastritis.

Byers and Jordan in 1962[7] interposed full thickness grafts from the canine stomach into the gallbladder. Despite bile flow over this mucosa, gastritis was not seen in biopsy specimens taken 1 to 12 months later. Belowski[5] noted peristomal gastritis when bile or pancreatic juice, or both, were in contact with the normal canine stomach. Lawson compared histologic changes following gastric resection with gastroduodenostomy and gastrojejunostomy.[36, 38] After gastric resection and gastroduodenostomy, microscopic changes were minimal and limited to the gastric mucosa around the anastomoses. After resection and gastrojejunostomy the changes were more severe and extended half way up the gastric remnant. The changes included atrophic gastritis at the antral fundic junction, epithelial proliferation in the fundus, and increased mitosis. Lawson then separated biliary and pancreatic secretions to study the effects of each on the gastric mucosa.[37] In these experiments gastric resection was not done. Results showed minimal histologic changes with each secretion and maximal changes with both at 100 and 200 days after surgery.

Several studies have isolated portions of the stomach on a vascular pedicle and interposed them in the jejunum.[13, 20, 21] These grafts were then exposed to bile, pancreatic secretions, or upper intestinal secretions (including bile and pancreatic juice). Again, the greatest changes (only microscopic) occurred when the stomach mucosa was exposed to all secretions.[37, 42] The histologic changes included gastritis and a decrease in the chief and parietal cells.

In all animal experiments no clinical symptoms accompanied the histologic changes. Lawson then demonstrated that the histologic

changes could be reversed by diverting these secretions from the stomach.[39] A Roux-en-Y anastomosis placed 60 cm from the gastric stoma was used.

Clinical Studies

Despite the limitations of experimental models, clinical evidence supports the existence of reflux gastritis as a distinct entity. Roux described relief of bile vomiting after construction of a Y anastomosis.[50] In 1951 Wells and Johnson reported 21 cases of postgastrectomy problems. Bile reflux and vomiting were prominent features in eight patients.[57] They postulated that this was due to a kink or twist of the afferent limb where it joined the lesser curvature of the stomach. The vomiting itself was perhaps due to retraction or incompetence of the cardia. Relief was obtained by dividing the afferent limb and implanting it 25 cm distal to the stoma on the efferent limb. In 1962 duPlessis reported 12 cases of epigastric pain, bile vomiting, and atrophic gastritis that developed 2 to 23 years after gastric surgery.[24] In all 12 patients symptoms were relieved after construction of a Roux-en-Y anastomosis.

A most unusual study was reported by Toye and Williams in 1965.[54] A 56-year-old man had severe bile vomiting 8 years after a gastrc resection; biliary colic and gallstones had developed. At the time of cholecystectomy, a tube was placed in the afferent limb and was used for subsequent infusions of saline or "bile" (actually bile, pancreatic, and duodenal secretions). After saline infusion, fullness was noted. When "bile" was infused, nausea and fullness were observed. The infusions were repeated with contrast material, and when the bile and radiooopaque mixture were infused the afferent limb was seen to empty into the stomach which then became dilated and did not empty immediately. Bile vomiting followed. This study refuted the then prevailing concept that bile vomiting was due to the afferent limb syndrome and sudden release of an afferent limb kink expulsed bile into the stomach.[43] Toye and Williams suspected the delayed gastric emptying was due to stasis induced by "bile in the stomach." This was corrected by converting a Billroth II anastomosis to a Billroth I anastomosis and interposing an isoperistaltic jejunal segment.

PATHOPHYSIOLOGY

Despite the preceding clinical observations, our understanding of the pathophysiology of reflux gastritis is still not agreed upon. Obviously the presence of bile and the alkaline pH of the intestinal and pancreatic secretions incriminates these factors.

Gastric aspirates contain bile in 60 per cent of normal persons, 89 per cent of duodenal ulcer patients, and 97 per cent of gastric ulcer patients.[34] That bile and bile salts may be injurious to the gastric mucosa has been shown by several experiments. Davenport's studies on the gastric mucosal barrier showed that the detergent actions of bile and bile salts could break the lipid membrane of gastric mucosal cells.[17, 18] These detergent properties are due to bile salts and lysolecithin. When this bar-

rier was broken, acid back diffused into the mucosal cell, and pepsin, sodium, water, and protein diffused into the lumen from the cells. The increased concentration of the diffused hydrogen ion into the cell was followed by histamine release. This resulted in capillary dilatation, increased permeability, and gastric mucosal hemorrhage.

The concentration of bile salts and bile acid conjugates in the gastric aspirate of patients with gastric ulcer is greater than in patients with duodenal ulcers or normal stomachs.[34, 47] Ivy et al.[32] postulated that the high concentrations of bile salts in the stomachs of gastric ulcer patients were responsible for the back diffusion of hydrogen ions leading to the development of gastritis or gastric ulcers. Bile salts may release gastrin from the gastric antrum.[4, 44] Gastrin increases acid secretion which may be harmful particularly when the "barrier" is broken. Conversely, gastrin is the trophic hormone to the gastric mucosa and increases the incorporation of protein into the mucosa.[33] It tightens the mucosal cell bridges and may prevent back diffusion of acid. Whether these effects of bile salts in man are pharmacologic or pathologic is unknown. However, the injurious effects of bile have prompted Silen to call it "malevolent" gall.[52]

Other than histologic changes, information on the effects of pancreatic juice and succus entericus on the gastric mucosa is limited.[20, 37] Certainly the pH of the resected or vagotomized stomach may enhance proteolytic activity of pancreatic enzymes, but whether this does happen is speculative.

Little attention has been paid to the gastric mucosa, pepsin, and acid. Why severe and chronic histologic changes may exist without symptoms in some patients and why minimal histologic changes exist with severe symptoms in others is not known. Only recently have cellular enzymes and function been studied in the gastric mucosa.[41] Another factor to consider is gastric stasis which may follow vagotomy.[19] This allows refluxed secretions to remain in contact with the gastric mucosa for long periods of time. Stasis may also allow overgrowth of bacteria with deconjugation of bile salts. These products may be injurious to the mucosa.

In most cases, the pathophysiology of reflux gastritis is due to many factors including bile acids and bile salts, pancreatic secretions, and succus entericus. These react on an altered gastric mucosa to produce gastritis. Continued exposure alters the gastric mucosal barrier to allow back diffusion of hydrochloric acid. For those few patients in whom the syndrome develops without previous surgery, abnormalities of the pyloric sphincter may be important, as has been proposed in the etiology of gastric ulcers.[26, 29]

CLINICAL PRESENTATION

The triad of bile vomiting, epigastric pain unrelieved by antacids or foods, and weight loss is present in 70 to 95 per cent of patients. The onset from the the time of gastric surgery varies from 1 week to 45 years. In a retrospective review of 119 patients with postgastrectomy

bile vomiting, Griffiths[27] noted the onset of this in the first 3 months after surgery in 65 per cent of patients. Only 7 per cent had symptoms develop 4 or more years after surgery. Of interest was that 50 per cent of symptomatic patients had symptoms for at least 4 or more years before a correct diagnosis was made. Some have suggested a longer delay in presentation after gastroenterostomy than after gastric resection.[56] Whether this is due to a greater susceptibility of corpus or fundic mucosa or protection by an intact antral mucosa is not known.

The epigastric pain is unrelieved by antacids or alkali and is thus differentiated from a marginal or duodenal ulcer.

The weight loss varies but may be 60 or more pounds (27.3 kg.).[30, 56] This considerable loss is due to limited oral intake because of the abdominal pain and vomiting.

Iron deficiency anemia caused by gastric hemorrhage has been emphasized by vanHeerden et al.[56] and by Mackman et al.[40] The presenting symptom of melena is usually due to blood loss through the gastric mucosa. Less commonly, hematemesis or even acute massive hemorrhage may develop.[56] Anemia may be present in 25 per cent of patients.

Dysphagia is present in less than 12 per cent of patients.[22] This is usually due to esophageal changes secondary to reflux and inflammation or subsequent stricture formation. An incompetent gastroesophageal sphincter mechanism, gastric stasis, and decreased gastroesophageal sphincter pressure may facilitate this reflux.

Diagnosis

When the diagnosis is suspected, endoscopy and barium roentgenography are done. Acid secretory studies may also be performed but these are not a specific diagnostic test.

Endoscopy

The definitive macroscopic diagnosis is made by endoscopic examination of the stomach and anastomotic area. The changes are quite variable. A beefy red, edematous, hemorrhagic gastric mucosa that is bile stained is present in severe cases and edema and erythema is seen in less severe cases. At least one report has correlated the severity of the endoscopic findings to the clinical syndrome, but others have not commented on this or have found no correlation. It is important to observe whether these changes are on the gastric or intestinal side of the anastomosis. In marginal ulcer, the gross changes occur on the intestinal side of the anastomosis; in reflux gastritis the changes take place on the gastric side.

An endoscopic biopsy of the most inflamed segment is performed. Microscopic findings will vary, depending on the severity and length of time the disease has been present. In mild cases chronic inflammatory changes, edema, and ulceration of the mucosal glands occur. Elongation and a corkscrew appearance of the mucosal glands as they extend to the lamina muscularis mucosa are seen (Fig. 1). In more severe cases gastric ulceration with exudate and polymorphonuclear cells on the mucosal surface are seen, with a decrease in the number of chief and parietal cells (Fig. 2). The atrophic gastritis progresses and the mucosal cells ap-

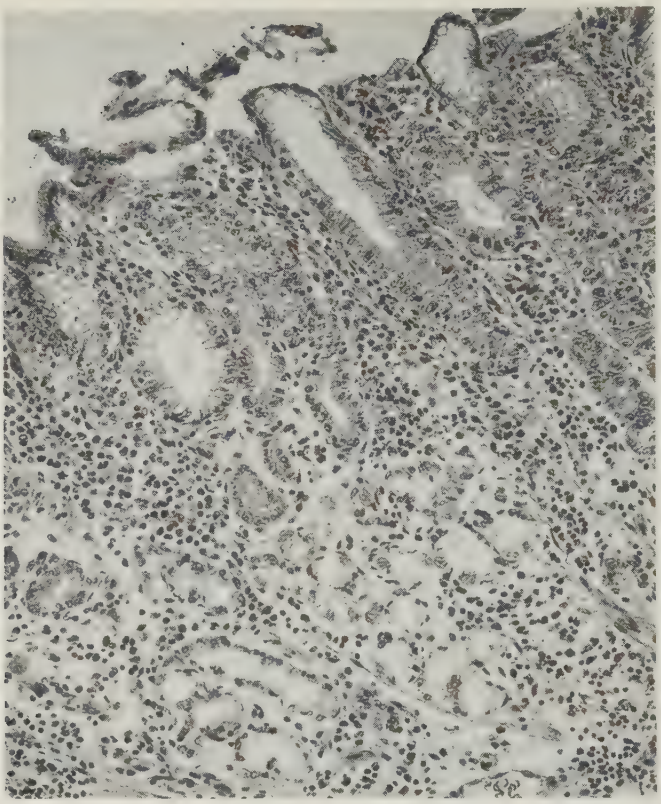

Figure 1. Biopsy of reflux gastritis. Chronic active gastritis of moderate severity. The lamina propria is suffused with plasma cells, lymphocytes, and polymorphonuclear leukocytes. The gastric epithelium demonstrates mild dysplastic changes secondary to the inflammatory process. Hematoxylin and eosin, ×64.

pear as large goblet cells of the intestinal mucosa. This is called intestinalization of the mucosa, and is characteristic of long-standing disease.

Barium Studies

Barium roentgenograms of the stomach are of limited value. They may reveal a large dilated stomach due to a previous vagotomy or bile and intestinal secretions in the stomach. Rarely, a large gastric ulcer is demonstrated. Thorfinnson and Brow[55] reviewed 30 cases of reflux gastritis; ten had abnormal roentgenographic changes. These changes were nonspecific, enlarged folds in the gastric remnant with most severe change near the anastomosis. In most cases these enlarged folds were due to edema. In only one instance was a gastric ulcer detected. Barium contrast studies will also exclude mechanical obstruction of the afferent or efferent limb.

Psychological Testing

A recurring suspicion that anxious "neurotic" patients are prone to this disorder is noted in many papers, but whether this is anecdotal or

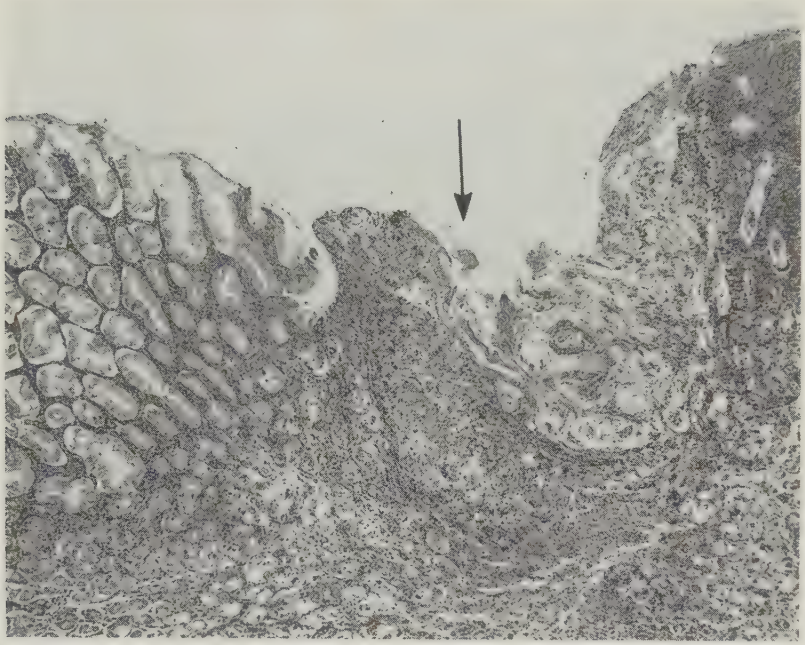

Figure 2. Biopsy of reflux gastritis. Superficial erosive gastritis with necrosis, hemorrhage and acute inflammation. Hematoxylin and eosin, ×64.

factual is not known. Our evaluation does include a screening psychological test on all patients with postgastrectomy disorders. Of 17 patients who underwent psychological evaluation, abnormal tests were found in 13.[56] There was no correlation with the end result in the patients with abnormal tests as four of 13 had poor results.

Acid Studies

The diagnostic value of gastric acid determinations in this entity has not been shown. Diminished values (< 2 mEq per hr) may be due to (1) the previous gastric operation, (2) back diffusion of acid through the gastric mucosa, or (3) neutralization of gastric acid by the alkaline secretions.

Most studies have shown hypochlorhydria or achlorhydria[30, 56] in basal and stimulated determinations. All the remedial operations for reflux gastritis are potentially ulcerogenic, and from a practical standpoint, adequate resections and vagotomies should be confirmed at surgery.

MEDICAL TREATMENT

Because the onset and course of reflux gastritis are unpredictable, the natural history of this disease is not known. Medical treatment has consisted of antiulcer regimens,[57] cholestyramine,[2] and occasionally me-

toclopramide[19] and hyperalimentation.[1] Despite their limited value, medical treatment should be tried first.

Antiulcer Regimen

Although antacids and antispasmodics have been widely utilized, their role and effect remain questionable. Because the secretions are alkaline or neutral, and because stasis may also be present in the gastric remnant, antacids and anticholinergics have limited value. If hyperacidity does exist, a better rationale would exist for the use of these drugs. Aluminum hydroxide may increase the absorption of bile salts, and this drug in combination with cholestyramine may be of benefit.[58]

Cholecystyramine (Questran)

Cholestyramine is an ion exchange resin that directly binds bile salts in the intestinal lumen and decreases the bile salt and bile acid pool.[2] The usual dosage has been a 4 gm packet 1 hour after meals and at bedtime. Ayuolo first suggested that this drug be used in postgastrectomy syndromes.[2] He described its value, particularly for diarrhea but did not expressly use it for bile vomiting. In 11 of 13 patients a good state of health returned.

At least three papers have commented on the results of cholestyramine in this disease. Eckstam et al. noted a good clinical response in ten of 20 patients in whom this drug was used.[25] Herrington et al. noted a poor response in ten patients.[30] At least one instance of symptomatic and histologic improvement has been recorded.[35] Most reports mention dissatisfaction or limited success with this drug.

Metoclopramide

Since gastric stasis due to a previous vagotomy or bile in the stomach may prolong the time that the refluxed secretions remain in contact with the gastric mucosa, some investigators have suggested using drugs which decrease the emptying time of the stomach.[19] Metoclopramide acts directly on the antrum to promote smooth muscle contraction and decrease the emptying time. Its effectiveness and value have been emphasized by Davidson and Hersh. They demonstrated its salutory effects in reflux gastritis; seven of 22 patients with reflux gastritis had stasis. The symptoms were not improved by a Roux-en-Y conversion until metoclopramide was added.[8]

Parenteral Nutrition

A trial of total parenteral nutrition to promote gastric healing was suggested by Anderson and Boyce[1] to help differentiate this syndrome from other causes of pain including functional causes or anxiety. It has not gained widespread acceptance for this reason, but may be a valuable preoperative adjuvant for nutritional reasons.

SURGICAL TREATMENT

The variety of operations employed for reflux gastritis attest to the fact that this condition may be satisfactorily treated in several ways

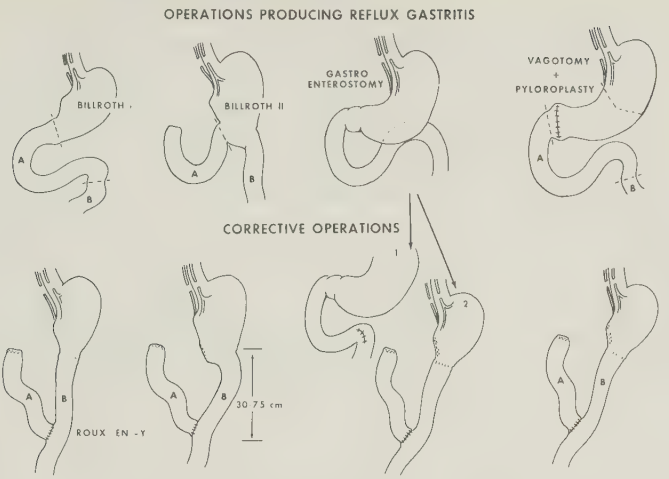

Figure 3. Operations that produce and correct reflux gastritis.

(Fig. 3). The two operative principles are (1) the upper intestinal, biliary and pancreatic secretions should be diverted from the stomach into the jejunum, and (2) marginal ulcers should not develop because of this diversion. Four operations have been employed, three of which are satisfactory. These are shown in Figure 4. They are (1) an entero-enteroanastomosis, (2) a Tanner procedure, (3) an interposed isoperistaltic jejunal segment (Henle loop), and (4) conversion to a Roux-en-Y anastomosis. Trial and error has shown that an entero-entero-anastomosis is unsatisfactory because the secretions are not totally diverted from the stomach. In our series only two of four patients were relieved with enteroanastomosis. I prefer the Roux-en-Y conversion. I use a stapling instrument

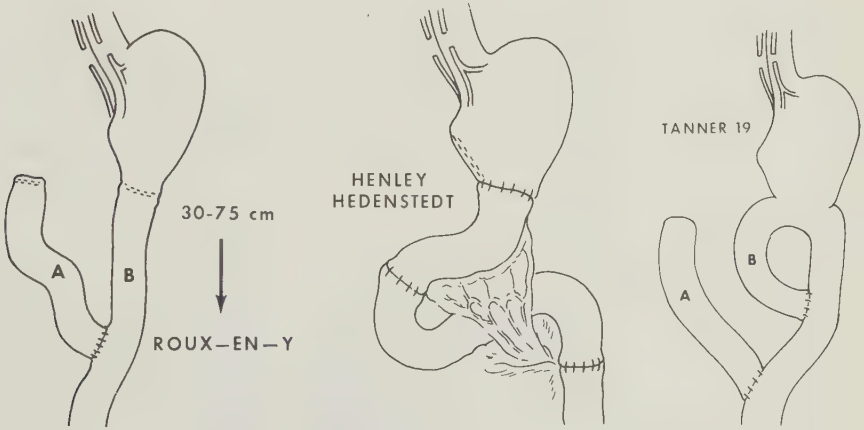

Figure 4. Operations used to correct reflux gastritis.

Table 1. *Results of Surgery for Reflux Gastritis*

AUTHOR	YEAR	NUMBER OF PATIENTS	ROUX-EN-Y	HENLE LOOP	TANNER	MISCELLANEOUS*	MORTALITY	RESULTS†	FOLLOW-UP
Wells and Johnson	1951	21	21					all I	
duPlessis	1962	12	12					all G	
Toye and Williams	1965	8		8				all E	
Coppinger et al.	1973	26	26				1/26	22–G 3–F	3 mo to 3 yr
Butterfield et al.	1973	4	1	3				all E	
Pyrtek and Barthus	1973	10	4		2	1		all G	
Joseph et al.	1973	11	10		1			all E	1 to 8.6 yr
vanHeerden et al.	1974	49	31	12	5	1		27–E 8–G 14–P	1 mo to 5+ yr
Eckstam et al.	1974	20	20				1/20	10–E 5–I 1–P	

Drapanas and Bethea	1974	24	15	3	5	1	1/24	2–E 1–G 1–P	3 mo to 4 yr
Herrington, et al.	1974	48	27	20		1		32–E 14–G 1–P 2–F	6 mo to 9 yr
Brooke-Cowden et al.	1975	17	16	1				13–G to E 1–S 6–P	
Davidson and Hersh	1975	22	21	1				9–G 7–F 6–P	
Cooperman, Ohme, et al.*	1976	35	29	2		4	1/35	19–E 4–G 8–P	1 mo to 9 yr
		307	233	50	13	8			

*Includes enteroanastomoses, takedown gastrojejunostomy, and conversion of Billroth II to Billroth I.
†E = excellent, G = good, F = fair, P = poor, I = improved.

to further simplify this operation. The afferent limb is stapled and divided and imbricated at the gastric junction.

How far from the gastric stoma should the anastomosis be made? There are many opinions on this. Wells and Johnson[56] used a distance of 25 cm with good results. The distance from the stomach has varied from 10 to 75 cm. Varying enthusiasm for each distance has been reported. At least one instance of recurrent bilious vomiting has been reported when a 10 cm distance has been used. I prefer a distance of at least 60 cm. The reasons are twofold: first, 60 cm has proven satisfactory by clinical and endoscopic studies; second, this is the length of a "silk tie" found in the operating room.

To avoid a marginal ulcer, a vagotomy must be done or two-thirds of the stomach resected. In patients who have had a previous pyloroplasty, one can transect the duodenum distal to the pylorus and place an interposed jejunal limb between the duodenum and stomach or close the duodenum and drain as a Roux-y. I have had one instance in which the edematous antral mucosa prolapsed and obstructed the anastomosis. Most authors have advocated antrectomy in this instance, not only to avoid this rare complication, but because it is an effective antiulcer operation as well.

Results of Surgery

That complete diversion of bile, pancreatic, and upper intestinal secretions is followed by symptomatic relief and histologic evidence of healing has been shown by several studies.[3, 10, 11, 19, 22, 30, 35, 39, 46, 54, 56] The type of diversion is of less importance than the principle followed. The results of surgery are summarized on Table 1. After surgery, a variable weight gain is observed. Evaluating the success of these procedures has been difficult because the criteria are often subjective and the follow-up periods are often not stated or are relatively short.

Our data have been less optimistic because many patients with reflux gastritis had associated postgastrectomy symptoms. These persisted after surgery and limited the success of surgery. Of 35 patients treated by Roux-en-Y anastomoses, six had poor results. Although all had relief of bilious vomiting, continued abdominal pain, diarrhea, and dumping marred this improvement. To further confuse evaluation, good results have been reported even though bile has been seen in the stomach after a 75 cm Roux-en-Y loop was constructed.[25]

Histologic Examination

Nearly all reports that have compared preoperative and postoperative biopsy specimens have shown significant improvement after surgery. Improvement occurs as early as 1 week postoperatively, although histologic evidence of healing may continue for months. As the gastric mucosa becomes normal its secretory function returns to normal as well. Achlorhydria and hypochlorhydria revert to normosecretion after corrective surgery.[39]

SUMMARY

1. The syndrome of reflux gastritis is produced by the actions of bile and upper intestinal and pancreatic secretions alone or in combination on an altered gastric mucosa.
2. The triad of epigastric pain unrelieved by antacids, bilious vomiting, and weight loss, particularly after a gastric operation should make one suspect this syndrome. Anemia due to loss of blood and dysphagia occur less frequently.
3. The definitive diagnosis is made by endoscopy. Barium studies are of less value. Acid secretory studies are not diagnostic and are of academic interest.
4. Medical treatment utilizes antacids and cholestyramine alone or together. Good, long-lasting results with these are infrequent. Despite these results, medical treatment should be tried first.
5. Surgical treatment consists of diversion of the biliary and upper intestinal secretions from the stomach and doing a vagotomy with or without a distal gastric resection to prevent a marginal ulcer from developing.
6. The two most popular operations are a Roux-en-Y diversion or interposed peristaltic jejunal limb. The simplicity of the former has made this more popular with most American surgeons.
7. The results of surgery are good to excellent in 75 to 95 per cent of cases. Relief of symptoms, improvement in histologic and secretory studies, and weight gain should be anticipated.
8. Less than optimal results are reported when the surgical diversion has not been total, gastric stasis persists, or other postgastrectomy sequelae accompany reflux gastritis.

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Postvagotomy Diarrhea

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A change in bowel habit occurs in about two-thirds of patients after truncal vagotomy. Many are pleased with the change from preoperative constipation to one or two soft stools daily. Others are bothered for a time by more frequent stools, but in most this gradually subsides so that by 3 months, it is no longer a problem. In a few patients, the diarrhea does not subside and they consider the operation a failure even though the ulcer has been cured.

Chronic postvagotomy diarrhea occurs in two forms—continuous, and episodic. In the continuous form, the patient essentially never has normal bowel function but passes only many watery stools daily. Some weight loss is the rule. In the more common episodic form diarrhea attacks recur at intervals of days or weeks, with normal bowel function in the interim. During the attacks there is characteristically extreme urgency and sometimes incontinence. Since the onset of the attacks is sudden and unpredictable, this is a serious economic and social handicap. The episodic form is associated with dumping in about one-half of patients. Weight loss is uncommon.

HISTORY

Dragstedt and associates[10] first called attention to postvagotomy alteration in bowel habit in 1947. Their first patients had undergone transthoracic vagotomy without a drainage procedure. Twenty-five of 61 patients so treated had a change in bowel habit but in 18 the effect was slight and transitory. In seven patients, moderately severe diarrhea continued for up to 5 weeks after the operation. Dragstedt and associates speculated that removal of the antiseptic action of the free acid of the gastric juice probably made these patients more susceptible to diarrhea of bacterial origin. They also noted a correlation between gastric retention and diarrhea, and as further evidence on this point stated that in their 64 patients with duodenal ulcer in whom an abdominal vagotomy

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plus gastroenterostomy was performed, slight and transitory diarrhea was encountered in only four patients. As the popularity of vagotomy rapidly spread, it quickly became obvious that patients with vagotomy plus gastrojejunostomy were also subject to severe diarrhea. It is now recognized that any surgical intervention on the stomach – pyloroplasty or gastrojejunostomy with or without vagotomy; resection, either Billroth I or Billroth II, with or without vagotomy; truncal, selective or parietal cell vagotomy – may be followed by diarrhea. The incidence however is different with different procedures and sheds some light on the cause(s) of the diarrhea.

INCIDENCE

The incidence of diarrhea after truncal vagotomy has been reported to be from 2 to 68 per cent.[17] Lack of a useful, widely accepted definition of what constitutes diarrhea probably is more responsible for such variability than any great difference in incidence. For example, Harkins' group reported in 1963 an incidence of diarrhea of 68 per cent.[15] Of this report, Nyhus said recently "We obviously overinterpreted 'change in bowel habit' as diarrhea."[21]

The Leeds/York trial of elective surgery for duodenal ulcer provided some interesting comparative data for three different ulcer operations.[13] Five to 8 years after operation, 21 per cent of patients with gastroenterostomy and truncal vagotomy had mild to moderate diarrhea and 5 per cent severe diarrhea; after vagotomy and antrectomy, 20 per cent had mild to moderate and 3 per cent severe diarrhea; after subtotal gastrectomy, 5 per cent had mild to moderate and 1 per cent severe diarrhea. Goligher defined the mild to moderate diarrhea as "mild and episodic and certainly imposed no real inconvenience." Of the severe classification he stated that because it was episodic and lasted for a day or so every 3 or 4 weeks, it only occasionally proved a handicap, depending on the patient's occupation.

If a more stringent definition of severe diarrhea is used, the incidence is much lower. McLoughlin et al.[20] studied 2058 patients who had undergone truncal vagotomy in the Merseyside Regional Health Authority area. They defined severe diarrhea as the persistent passage of six or more bowel actions per day associated with urgent desire to defecate and the passage of unformed stools. Only 14 patients met these criteria – an incidence of 0.7 of 1 per cent. Herrington et al.,[16] in their personal series of over 3500 truncal vagotomies, found only four patients in whom the diarrhea was sufficiently severe to warrant an attempt at operative correction.

Many authors have found that diarrhea is less frequent after selective vagotomy than after truncal vagotomy. Johnston et al.[17] collected 13 reports from the literature that compared the two procedures. Twenty-four and six-tenths per cent of 1130 truncal vagotomy patients had diarrhea; 12.3 per cent of 790 selective vagotomy patients had diarrhea. They also reported on the incidence of diarrhea in their study at

Leeds/York of three types of vagotomy. At the one-year follow-up, diarrhea was recorded in 24 per cent of patients after truncal vagotomy and pyloroplasty, in 18 per cent after selective vagotomy and pyloroplasty, but in only 2 per cent of patients after highly selective vagotomy without a drainage procedure.

PATHOPHYSIOLOGY

Bacterial colonization of the upper small intestine after vagotomy was suggested by Dragstedt and Woodward[11] in 1951 as a possible etiology of postvagotomy diarrhea. More recently, because of their known association with the steatorrhea of the blind loop syndrome, the fecal type of anaerobic organisms has become suspect. Bacteroides has been the prime suspect because of the ability of this organism to deconjugate bile salts.

Many patients with postvagotomy diarrhea have been treated with antibiotics to no avail, in contrast to the marked benefit of antibiotic therapy in the blind-loop syndrome. Also, there is no correlation between the incidence of postoperative achlorhydria and diarrhea—many patients with achlorhydria have no diarrhea. Browning, Buchan, and MacKay[5] studied the bacterial flora of the upper small intestine of 32 patients with diarrhea 4 years following truncal vagotomy and drainage. A comparison was made with 24 comparable patients without postvagotomy diarrhea. The incidence of bacterial colonization of the upper small intestine was no different in the two groups. It seems unlikely that bacterial colonization plays a major role in the postvagotomy diarrhea of most patients but has been implicated recently in postvagotomy patients with previously unsuspected immune deficiencies. McLoughlin et al.[20] found six such patients in their study of 2058 truncal vagotomy patients. These six patients had no measurable serum levels of IgA, had chemical evidence of malabsorption, normal jejunal biopsies, and heavy growth of both aerobic and anaerobic organisms on culture of jejunal aspirate.

Structural abnormalities of the intestinal mucosa resulting from vagal denervation that might cause malabsorption and diarrhea have been diligently searched for by many investigators. Though Ballinger et al.[3] found villus atrophy in dogs after vagotomy, similar changes are not demonstrable in man with postvagotomy diarrhea—their mucosae are normal.[4] There are, however, several case reports of patients in whom nontropical sprue has been unmasked by vagotomy. They have villus atrophy and when put on a gluten-free diet become symptom-free. Such patients are the exception, not the rule, in postvagotomy diarrhea.

Lactose intolerance also accounts for a few patients with postvagotomy diarrhea. Intestinal lactase normally hydrolyzes ingested lactose into its constituent monosaccharides, glucose and galactose. With intestinal lactase deficiency, unhydrolyzed lactose within the bowel exerts an osmotic effect resulting in abdominal distention, cramps, and diarrhea. There is some evidence that gastric operations may reduce intestinal

lactase activity.[14] Condon, Westerholm, and Tanner[8] examined 50 patients who developed various combinations of milk intolerance, dumping and diarrhea after partial gastrectomy or vagotomy with drainage. Eight of the 50 did have lactose malabsorption and responded to a lactose-free diet.

Division of the parasympathetic nerve supply to the pancreas might be expected to diminish the exocrine response of that gland, with faulty digestion and steatorrhea. There is little evidence, however, that digestion and absorption are interfered with sufficiently to be of clinical importance. If steatorrhea is defined as fecal excretion of more than six grams of fat daily, then a considerable number of patients has steatorrhea after gastric surgery.[12] But such minimal steatorrhea is of no consequence and occurs independently of diarrhea – the same number of completely asymptomatic patients have borderline steatorrhea as do patients with postvagotomy diarrhea.[18]

Vagal denervation of the stomach destroys the fine control of gastric emptying. Solids empty more slowly than normal but fluids or fluid-solid mixtures rapidly empty into the intestine. This is equally true for truncal or selective vagotomy with a drainage procedure. Parietal cell vagotomy by virtue of retained antral innervation and the absence of a drainage procedure preserves a more normal pattern of gastric emptying. Although postoperative changes in the direction of more rapid gastric emptying and small-bowel transit are much less pronounced after parietal cell vagotomy than after truncal or selective vagotomy with a drainage procedure, such changes do still occur.

Johnston et al.[17] administered a hypertonic glucose test meal to preoperative duodenal ulcer patients and to patients who had undergone the three types of vagotomy. Diarrhea was provoked in none of the preoperative patients, in 13 per cent of those who had undergone parietal cell vagotomy without a drainage procedure, in 60 per cent of those who had undergone selective vagotomy and pyloroplasty, and in 67 per cent of the patients who had undergone truncal vagotomy and pyloroplasty.

McKelvey[19] treated 16 patients with postvagotomy diarrhea with low-fluid meals, with the consumption of fluids between meals. With a mean follow-up of 9 months, 14 of the 16 had their diarrhea controlled or improved.

The loss of control of the gastric emptying of fluids may explain the difference in the incidence of diarrhea between parietal cell vagotomy and the other two types of vagotomy but does not explain the different incidence between selective and truncal vagotomy. Vagal innervation of the biliary tract may be the difference. This innervation is preserved in selective vagotomy but divided in truncal vagotomy.

The late Harold Burge and associates[6] evaluated symptoms in 100 patients after truncal vagotomy, in 73 patients in whom an attempt was made to do a vagotomy and leave intact the celiac division of the posterior vagus, and in 100 patients in whom the hepatic branch of the anterior vagus as well as the celiac branches of the posterior vagus were left intact. Those with an intact hepatic branch had a decreased in-

cidence of postvagotomy diarrhea. The reason was not apparent at that time.

Since excessive amounts of dihydroxy bile acids in the colon are known to stimulate water and electrolyte secretion and cause diarrhea, Allan et al.[1] evaluated their possible role in postvagotomy diarrhea. The fecal excretion of bile acids were measured in patients with severe, continuous postvagotomy diarrhea, patients with vagotomy and drainage operations but no diarrhea, and in normal control subjects. The bile acid secretion, particularly the hydroxy, were markedly higher in the diarrhea group than in the control group. Allan and Russell[2] subsequently carried out a double-blind controlled trial of cholestyramine, a bile acid-binding resin, in the treatment of postvagotomy diarrhea. Sixteen patients with severe continuous postvagotomy diarrhea received either 4 grams of cholestyramine per day for 2 months or a placebo for a similar time. A significant improvement was recorded in the eight patients receiving cholestyramine, but no overall improvement was observed in the placebo group.

Condon et al.[7] have successfully treated six patients with watery postvagotomy diarrhea with cholestyramine. The diarrhea responded completely to therapy, during which the stool content of water, sodium, potassium, and magnesium fell. Condon feels the mechanism of diarrhea is division of the hepatic fibers of the vagus resulting in a large flabby distended gallbladder, contraction of which expels increased quantities of bile salts, which swamp the resorptive capacity of the small intestine and induce diarrhea by direct action on the colon. He suggests that cholecystectomy, by preventing large quantities of concentrated bile salts from suddenly entering the gut, might improve postvagotomy diarrhea.

The bile salts mechanism may explain the difference in incidence of diarrhea after truncal vagotomy and selective vagotomy which preserves the fibers to the biliary tract. Further work is needed.

PROPHYLAXIS AND MANAGEMENT

Prior to any elective ulcer operation the patient should be questioned closely concerning his bowel habits in an attempt to uncover borderline cases of lactose intolerance, gluten enteropathy, or IgA deficiency. If any of these is suspected, a work-up should be done; and if found, proper treatment instituted prior to operation. In patients with questionable need of an operation, the presence of gluten enteropathy or IgA deficiency would probably warrant deferring the operation.

Diarrhea occurs so commonly in the early postoperative period but is so commonly self-limited that efforts to discover the cause are usually not indicated. It is probably worthwhile however to advise postvagotomy patients to take their meals without supplemental fluids and to consume liquids between meals. Some surgeons do this routinely in all vagotomized patients. Symptomatic therapy such as lomotil, codeine, or paregoric is often helpful.

If the diarrhea persists beyond about 6 weeks and is a problem to the patient, a diarrhea work-up is in order. Since about one-half of postvagotomy patients with diarrhea have it in association with early dumping, this should receive attention first. The history alone often suffices for diagnosis but may need confirmation with upper gastrointestinal series and a provocative glucose meal. Symptoms of dumping with diarrhea and of diarrhea alone due to gastric incontinence but without dumping symptoms per se may be elicited by the glucose test meal. The management of dumping is discussed elsewhere in this symposium.

Next, the specific causes of diarrhea such as lactose intolerance, gluten enteropathy, and IgA deficiency should be evaluated even though this has been done preoperatively (v.s.).

Subclinical lactase deficiency may become apparent postoperatively because the rate of delivery of lactose into the bowel is an important determinant of the severity of symptoms.[8] Thus, with a postoperative stomach that is incontinent of fluids the ingested sugar is dumped into the small intestine faster than the disaccharidases can handle it. Most lactase deficient patients can relate ingestion of dairy products, particularly milk, to some combination of the following symptoms: nausea, abdominal bloating, cramps, flatulence, and diarrhea. In some patients symptoms are obscure or even absent and an oral lactose tolerance test is necessary for diagnosis. One hundred grams of lactose is given orally and the blood glucose determined as for an oral glucose tolerance test. Normally, digestion and absorption will lead to the same rise in blood glucose as will the ingestion of an equivalent amount of glucose or galactose. If the blood glucose does not increase more than 20 mg per 100 ml per cent following the ingestion of 100 gm of lactose, this flat lactose tolerance curve ordinarily represents lactase deficiency. If gastric emptying is slow, however, this may interfere with the diagnostic accuracy of the test and the test should be done by infusing 30 gm of lactose in 300 ml of water into the duodenum in 30 minutes. Symptomatic improvement can be expected when the offending lactose is removed from the diet. Often withdrawal of milk alone suffices; if not, then all dairy products should be eliminated from the diet.

Gluten enteropathy or celiac sprue (and many other names) may also be unmasked by gastric surgery, though on close questioning an antecedent history of occasional loose bowel movements can usually be elicited. Three criteria should be met to establish a definite diagnosis: evidence of malabsorption; an abnormal jejunal biopsy showing blunting and flattening of the villi as well as changes in the surface epithelium; clinical, biochemical and histologic improvement after institution of a gluten-free diet. It should be stressed to the patient that strict adherence to the diet is essential—even occasional minor transgressions are unacceptable.

If during the work-up of a patient with postvagotomy diarrhea a deficiency of serum globulins is found, this finding alone does not constitute a diagnosis of the diarrhea—less than one-half of patients with globulin deficiencies have any gastrointestinal abnormalities. Jejunal biopsy in symptomatic IgA deficiency is usually essentially normal but

may be flattened and resemble celiac sprue. The number of plasma cells is usually markedly reduced. Culture of the jejunal aspirate is essential to the diagnosis and in symptomatic patients should yield a heavy growth of aerobic and anaerobic organisms, and the urinary indican secretion is also markedly elevated. Treatment is with oral antibiotics. Injections of gamma globulin or fresh plasma may also be helpful. Some respond to a gluten-free diet.

Choleric enteropathy, attributable to the overly rapid passage of small bowel contents into the colon or to abrupt discharge of an abnormally large amount of concentrated bile from a distended gallbladder into the intestine, is thought to play a role in some patients with postvagotomy diarrhea. Diagnosis of this entity by quantitative analysis of the stools for bile acids is not practical in the usual hospital setting. Thus a diagnostic-therapeutic trial of cholestyramine, an exchange resin that binds bile acids is in order. Questran, 9 gm containing 4 gm of cholestyramine resin, is given three times daily, before meals. If choleric enteropathy is indeed the problem, amelioration of symptoms should occur within 2 weeks.

If all the above have been tried to no avail and the patient is still incapacitated by postvagotomy diarrhea, then an operation might be considered. There are anecdotal reports of patients who have been benefitted by changing a gastrojejunostomy to a pyloroplasty. It is difficult to see how this could be of significant value, however (for diarrhea that is, not dumping) and cannot be recommended.

Craft and Venables,[9] and independently at about the same time, Herrington et al.[16] have recommended reversal of a loop of jejunum for severe, unremitting, incapacitating postvagotomy diarrhea which has not responded to conservative therapy. Craft and Venables report on one patient, and Herrington et al. on seven patients in whom this was done. All eight patients were relieved of symptoms and continued to do well from 3 to 27 months after the reversal operation. The recommended length of jejunal segment to be reversed is 10 to 15 cm, and is best placed from 50 to 100 cm distal to the ligament of Treitz. If early dumping syndrome is the problem and the diarrhea only an associated symptom, then the reversed loop should be interposed between gastric remnant and duodenum.

Parietal cell vagotomy has been billed as the "vagotomy without diarrhea."[17] If it also proves to be the vagotomy without recurrent ulcers then it should be the procedure of choice as far as the prevention of the complication of postvagotomy diarrhea is concerned. In the meantime, selective vagotomy should ordinarily be preferred to truncal vagotomy since the selective is followed by diarrhea only one-half as often and is at least as good on all other counts.

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Stress Ulcers: Their Pathogenesis, Diagnosis, and Treatment

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Erosions of the gastroduodenal mucosa may occur acutely after major physical or thermal trauma, shock, sepsis, head injury, or the ingestion of a variety of chemical agents, such as aspirin and alcohol. It is customary to designate such lesions by the term "stress ulcers." Since acute ulcers have different morphologic characteristics, clinical manifestations, and underlying pathogenesis, it is helpful to consider their presence in the context of the clinical setting in which they occur. In this scheme, stress ulcers secondary to shock or physical trauma can be distinguished from those which follow head injury (Cushing's ulcer), burn (Curling ulcer), or drug ingestion (erosive gastritis). Superficial gastric erosions that occur after severe trauma, major operations with complications, or prolonged medical illness, usually occur in the fundus and body of the stomach. They are superficial and multiple with no evidence of chronicity. Cushing's ulcer, which occurs with intracranial tumor, head injury, or after cranial surgery, may involve esophagus, stomach, and duodenum. In contradistinction to other forms of erosive gastritis, acid secretion is usually high, possibly as a consequence of rise in intracranial pressure. Erosive gastritis induced by alcohol, aspirin, and other irritants, is exceedingly common as recognized by current frequent use of gastroscopy. In this review we will examine the evolving body of knowledge which provides insight into the etiology of stress erosions with the expectation of providing a better understanding of its pathogenesis and a more rational basis for the early recognition, treatment, and prevention of this serious condition.

INCIDENCE

Severely injured patients with multiple trauma are at high risk for developing erosive gastritis. Most clinical studies which do not employ routine endoscopy probably underestimate the incidence of this disease,

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since its recognition requires gastrointestinal bleeding or perforation. Lucas et al.[24] have shown by gastroscopy that the incidence of stress ulcer in 40 severely injured patients was 100 per cent. In a similar study at the Brooke Army Surgical Research Institute[9] of 29 patients with major burns, gastric erosions were found in 27 by sequential endoscopic examination. The majority of these patients had lesions within 72 hours after burn. Fortunately, only a small number of these patients demonstrated significant gastrointestinal hemorrhage. This low incidence of clinically detectable bleeding relates to the superficial nature of early lesions. As they penetrate deeper into the mucosa as a function of time, however, massive life-threatening hemorrhage becomes an all too frequent occurrence.

PATHOGENESIS

While the precise mechanisms involved in the development of stress ulcers are unknown, current evidence supports a multifactorial etiology. The following discussion will focus on our current hypothesis based on recent experimental observations.

The Presence of Luminal Acid

Hypersecretion of acid is an unlikely cause except in the pathogenesis of Cushing's ulcer. In fact, acid secretion has been normal or even low in most other forms of stress ulcer. On the other hand, it can be stated with certainty that some hydrogen ions are necessary for the development of stress ulcers, because all experimental models of this entity require a low gastric luminal pH.[6, 22, 27] The "no acid-no ulcer" dictum implied by this important piece of knowledge has led to the concept that buffering of intragastric contents may prevent post-traumatic erosive gastritis. There is an accumulating body of knowledge to support this point of view.

Ischemia

Clinically, most patients who develop stress ulcers have experienced shock from hemorrhage, sepsis, or cardiac dysfunction. Diminished mucosal blood flow is a common denominator in animal experiments which employ restraint, hemorrhage, or endotoxemia for production of erosive gastritis. Therefore, a decrease in mucosal blood flow seems to be a common manifestation during the developmental phase of these types of erosions. The focal nature of such lesions has suggested that decrease in mucosal perfusion may be the result of opening of submucosal arteriovenous shunts. This concept has recently been challenged by both histologic studies and quantitative measurements of mucosal blood flow.[14, 15, 21] Guth and Smith[21] failed to demonstrate submucosal arteriovenous shunts during normal, sympathetic nerve stimulation in rats. By using ^{42}K, Delaney and Grim[14] demonstrated that no more than 1 to 2 per cent of gastric blood flow passes through arteriovenous shunts in normal dogs. They have further shown that this

was not significantly changed during induced variation of blood flow by vasoactive drugs.[15] Recently Archibald et al. have confirmed this finding with radioactive microspheres in dogs under normal conditions and infusion of isoproterenol. Lastly we have demonstrated that there was no significant AV shunting during E. coli endotoxin infusion and hemorrhagic shock.[5] All of these data indicate that arteriovenous shunting is unlikely to play a significant physiologic role in the development of mucosal ischemia. The decrease in flow observed during hemorrhagic shock and endotoxemia is, therefore, a consequence of a restriction in blood flow to all layers of the gastric wall. Menguy and his colleagues[26] provide evidence that shock-induced ischemia results in profound decrease in gastric mucosal energy metabolism. The extraordinary vulnerability of gastric mucosal energy metabolism results from the tissue's lack of glycogen and its relative inability to utilize anaerobic glycolysis as an alternate source of energy. They propose that the decrease in energy metabolism in the gastric mucosa is the cause of rapid cellular necrosis occurring in this tissue during hypovolemic shock.

Gastric Mucosal Permeability

Exposure of gastric mucosa to alcohol, aspirin, and a variety of other substances known as barrier breakers, results in increased back-diffusion of hydrogen ions and disruption of the mucosal surface.[11, 12] Ingestion of these substances is also associated with a high incidence of erosive gastritis. The mechanism of even this flagrant form of ulcerogenesis is unknown, but may relate to a rapid change in mucosal intracellular pH or osmolarity, or may be the consequence of loss of surface taxis, or biochemical events within the lamina propria beneath the surface epithelial cells.[33] It has been suggested that cause-effect relationships exist between ischemia and disruption of the mucosal barrier. However, disruption of the gastric permeability barrier by aspirin, bile salts, and alcohol does not cause mucosal ischemia. In fact, we have shown that mucosal blood flow measured by gamma-labeled microspheres actually increases under such circumstances.[4] On the other hand, ischemia following hemorrhagic shock in dogs[27] and in subhuman primates,[31] and administration of vasopressin in dogs does not render the mucosa more permeable to secreted acid.[10, 18] We have also reported that intra-arterial infusion of E. coli endotoxin[5] does not disrupt the mucosal barrier in spite of development of gastric erosions. These observations indicate that general disruption of the mucosal barrier (as evidenced by increased back-diffusion of hydrogen ions) is not an essential component of the pathologic process of stress ulcer but, if present, may in itself lead to the syndrome. The most likely explanation is that a synergistic relationship exists between ischemia and back-diffusion of intraluminal acid. This has been supported by the work of DenBesten and Hamza[17] and Ritchie and his colleagues[31] in dogs and monkeys respectively, in which they demonstrated that shock coupled with exposure of the mucosa to bile salts and acid will lead to severe ulcers, whereas shock or bile salts alone only cause mild mucosal damage. This has led to the hypothesis that mucosal blood flow may be essential in

the disposal of back-diffused hydrogen ions. Under normal conditions, a small amount of hydrogen ions within the tissue may be rapidly cleared by blood flow, whereas erosions may develop when the ratio of mucosal blood flow to hydrogen ion back-diffusion is reduced in stressed subjects. Patients who are traumatized when acid, bile salts, aspirin, and alcohol bathe their gastric mucosa are probably at higher risk for developing acute ulcers than individuals who have a high intraluminal pH or are free from barrier breakers at the time of their accident.

This postulation certainly does not answer all questions as regards etiology of stress ulcer. For example, the role of environmental stress may possibly be an important factor in the genesis of acute erosions. However, the precise mechanism remains obscure in spite of a large amount of recent work in the area.[13, 29] What are humoral factors? It has been well established that physical stress, especially in association with shock, is accompanied by increased blood levels of catecholamines and cortisol. Although steroids potentiate the increased permeability of the gastric mucosa to hydrogen ions caused by bile salts, aspirin, and acetic acid, alone they do not cause disruption of the gastric mucosal barrier.[7] In fact, pharmacologic doses of steroids attenuate erosion formation in restrained rats.[23] The ulcerogenic potential of catecholamines has not been adequately studied. The focal nature of gastric erosion observed in clinical patients and in experimental animals[9, 27] has not been explored. It is possible that ischemia occurs at a focal site and that, indeed, back-diffusion in these areas may be intense, leading to the discrete multiple lesions so characteristic of the stress ulcer syndrome. Laboratory and clinical investigation continue in the hope that future understanding of these questions may lead to more precise ways of prevention and treatment of this devastating disease.

CLINICAL MANIFESTATIONS

Painless unexpected gastrointestinal bleeding from mouth or anus is the hallmark of stress ulcer. Although acute erosions may occur during or shortly after a traumatic incident, frank hemorrhage from these lesions is usually delayed for several days. Hematemesis and melena are of equal frequency. Clinical findings of associated illness or injury are often present. Peritonitis or other signs of severe sepsis may be in evidence and accompanied by varying degrees of respiratory, renal, cardiac, and hepatic failure.

Clinical manifestations of massive bleeding from stress ulcers relate to amount and rate of blood loss and the patient's general condition at the onset of the bleed. Occasionally recognition of the source of cardiovascular collapse is delayed in an already critically ill patient. The sudden occurrence of hypovolemic shock with rapid pulse, hypotension, and cool moist skin, should bring this diagnosis to mind in a patient at risk. A drop in urine output is one of the more sensitive indicators of low tissue perfusion in the absence of renal disease.

DIAGNOSTIC APPROACH

Before specific diagnostic procedures are undertaken to identify the source of bleeding, blood volume must be restored. Blood should be drawn immediately for determination of hematocrit, coagulation factors, and cross match. Preferably two large bore catheters should be placed in antecubital veins, one inserted to the level of the superior vena cava in order to monitor central venous pressure. Certain features can be assessed quickly such as the general state of health, heart rate and rhythm, blood pressure, respiratory rate, and skin color and moisture. A nasogastric tube should be inserted in order to detect the presence of blood, or its rate of accumulation within the gastric lumen. Patients who develop gastrointestinal hemorrhage postinjury or after an episode of shock or sepsis should be considered to have stress ulcerations until proven otherwise. An aggressive diagnostic approach should be taken to confirm the diagnosis. Delays due to fear of "disturbing clots" are not justified. In fact, the initial approach should include vigorous lavage of the stomach in order to clear its lumen of clots and old blood. There is controversy as to whether the wash solution (usually saline) should be cold or warm. Cold saline will decrease mucosal blood flow but disturb coagulation; warm saline will increase mucosal perfusion but enhance coagulation. We are not aware of a randomized control trial which might serve to resolve the controversy. Hot or cold, lavage appears to be associated with cessation of bleeding in about 80 per cent of cases. Conventional radiologic examination of the stomach and duodenum by barium is of little help, since lesions are too superficial to be detected by this method. Many patients are also too ill for an adequate barium study. Endoscopy, therefore, is the diagnostic procedure of choice, since it can be done at the bedside. The new fiberoptic esophagogastroduodenoscope offers a simple, safe, and relatively atraumatic way to make a specific diagnosis. Lucas et al.[24] have described the characteristics of stress ulcers by sequential endoscopic examination in 42 patients with severe trauma. The earliest changes include interspersed foci of pallor and hyperemia mostly located in the proximal stomach. These foci are initially small, shallow, punctate erosions which progress to petechiae by 24 hours. The erosions become deeper with marginal swelling and may involve the entire stomach by 48 hours.

The use of angiography in the diagnosis of stress ulcer is reserved only for those cases in which gastroscopy fails to demonstrate the bleeding site, or in which control of bleeding is to be gained by pharmacologic means.[1] In patients with massive, persistent bleeding, we arrange angiography at the same time that endoscopy is performed. In an occasional case, angiography succeeds in identifying the bleeding site, when endoscopy fails. The inconvenience, and relative risk and expense, however, has placed angiography in a secondary role in the usual mild to intermediate bleed from post traumatic gastritis.

In our experience, endoscopic findings in conjunction with the history, usually differentiates stress ulcer from other bleeding lesions, such

as reactivation of a chronic duodenal or gastric ulcer, or esophageal varices. An upper barium gastrointestinal study, however, is sometimes helpful in identifying other potential sources of bleeding.

TREATMENT

Once stress ulcers are associated with significant hemorrhage, mortality exceeds 50 per cent, indicating the lethal nature of this complication. Therefore, early recognition and prevention of deeper penetration of erosions is important. All patients should be given adequate supportive care for shock and sepsis with careful monitoring of the extent of hemorrhage. Patients with bleeding should be checked for coagulation defects, and specific clotting abnormalities should be corrected. Fresh whole blood is used as part of volume replacement for every sixth unit of blood transfusion. If fresh blood is not available, fresh frozen plasma and platelet packs may be helpful. Gastric aspiration is indicated to remove duodenal content which may have refluxed into the stomach as a result of adynamic ileus, since bile salts and pancreatic juice are injurious to the gastric mucosal membrane.[31]

The use of antacids in the treatment of stress ulcers has been reported as being effective in a clinical study of a small number of patients.[8] However, these observations were not made in a properly controlled, randomized study; hence, they must be regarded as inconclusive. Silen[32] suggested the instillation of 15 ml of any commonly employed liquid antacid via the gastric tube, with subsequent clamping of the tube for 15 to 20 minutes. Continuous gastric aspiration is then begun. After 1 hour of suction, the pH of the gastric aspirate is tested with pH paper. If the pH is above 4.5, suction can be repeated for another hour. If the pH is below 4.5, another dose of antacid is instilled. Since it is safe and simple, we have been using antacid on patients with stress ulcers, in the absence of massive hemorrhage. Since the neutralizing capacities of commonly used antacids vary significantly, we prefer to use the potent ones such as Ducon or Mylanta II.

There has been recent enthusiasm for pharmacologic control of stress ulcer bleeding by continuous intra-arterial infusion of vasoconstrictors into the gastric blood supply.[1] While different vasoconstrictors have been used by several authors, vasopressin has been the most commonly used. Since vasopressin should be infused selectively into the left gastric artery, subselective catheterization of these vessels is required. The value of this technique has been encouraging;[1] however, it has not been established by a prospective well controlled study. We use this therapy when conservative management fails to control bleeding. The experience gained to date suggests that the intra-arterial infusion of vasoconstrictors can control stress ulcer bleeding in most cases.

Transendoscopic control of upper gastrointestinal bleeding is currently in the development stage. Gaisford reported on the transendoscopic control of bleeding in 33 patients from a variety of mucosal lesions including stress ulcers. Bleeding was immediately controlled in all but

Table 1. *Literature Review of Operative Results (1949–1971)**

PROCEDURE	NUMBER OF PATIENTS	NUMBER WITH REBLEEDING	PER CENT	NUMBER OF DEATHS	PER CENT
Exploration only	27	16	59	13	48
Subtotal gastrectomy	95	50	51	32	38
Vagotomy and gastrectomy	54	9	17	13	24
Vagotomy and drainage	177	52	29	41	23
Vagotomy and drainage w/suture ligation (present series)	21	2	9.5	5	24
Total gastrectomy	12	0	0	2	17

*Updated from Drapanas et al. (modified from Wilson, W. S., Gadacz, T., Olcott, C., III, and Blaisdell, F. W.: Superficial gastric erosions: Response to surgical treatment. Am. J. Surg., *126*:136, 1973.).

two who subsequently required an operation for recurring hemorrhage. The value of such an approach is obvious and no doubt will receive extensive study during the ensuing years. However, as the complications from this procedure are not yet known, it is too early to recommend it for general use in the management of bleeding stress ulcers.

In most patients, bleeding stops with the aid of saline lavage, or selective arterial infusion with vasoconstrictors, but a small percentage of patients will continue to bleed and will require surgery. As a review of reported results of surgical therapy reveals little solid evidence to support the use of one type of operative procedure or another, the choice of procedure is open to question. Several recent surgical series[19, 34] seem to favor vagotomy and pyloroplasty as an initial operation, but there are too many variables in this large collection of data to allow a definite conclusion to be made (Table 1). On the other hand, Menguy and his associates[25] have reported unsatisfactory results for vagotomy and pyloroplasty because bleeding continued or recurred in a large number of patients. Therefore, they advocate that the best results in terms of control of bleeding were obtained with total and near total gastrectomy. In our own experience, we have had fairly satisfactory results with vagotomy and pyloroplasty and oversewing the bleeding ulcers as an initial operation for bleeding stress ulcers. Subtotal gastric resection is reserved for those in whom bleeding continues after the initial operation. The San Francisco experience reported by Wilson and his colleagues[34] would appear to support this point of view.

PREVENTION

Since results of all forms of therapy are poor, prevention of development and progression of stress erosions would appear to offer the most rational approach to the management of this disease. Many drugs and chemicals have been shown to protect animals from the development of

stress ulcers, but none have been tested in patients. The following methods of prevention have been advocated in patients.

Buffering of the Luminal Content

Since stress ulcer will not occur if the luminal content is buffered, neutralizing intraluminal acid with antacid would be expected to prevent its development.[32] However, the effectiveness of this treatment has not been tested in a large group of patients with proper control. This is probably due to the difficulties of maintaining luminal pH neutral by conventional methods.

Inhibitors of Acid Secretion

The use of inhibitors of acid secretion, such as prostaglandins and the H_2 receptor antagonists, metiamide or cimetidine, has been reported to reduce the incidence of stress ulcer in animal experiments.[20] So far, these observations have not been extended to clinical studies, and it is an area that undoubtedly will receive more attention in the ensuing year for the prevention of stress ulcer.

Others

Methods to augment gastric mucosal regeneration, such as administration of vitamin A, growth hormone, and hyperalimentation, have been suggested to protect mucosal injury from stress. Several recent studies have demonstrated the importance of vitamin A in preserving the function and promoting the normal proliferation of mucous cells in the gastrointestinal tract in animals,[3, 16, 30] a result which has not been reproducible by other investigators.[28] Clinical studies have also reported a reduction in stress ulcers developing in patients receiving large doses of vitamin A.[3] However, the presence of stress ulcers in these studies was not confirmed by endoscopic examination, and the accuracy of diagnosis is therefore questioned. Growth hormone, which stimulates RNA and protein synthesis, has been shown in animals to partially protect the gastric mucosa from stress-induced injury. A small clinical study has shown that in six of eight patients with stress ulcers, the bleeding was controlled by human growth hormone.[35] The protective effect of intravenous hyperalimentation on gastric mucosal regeneration has been studied in a small number of patients undergoing abdominal aortic surgery.[2] Although it has shown that positive nitrogen balance was achieved in hyperalimented patients, its effect on mucosal regeneration and gastric secretion remains inconclusive. These observations certainly need to be extended to a large number of patients in a prospective study. At the present time we are reluctant to recommend the use of these methods for the prevention of stress ulcers.

SUMMARY

Stress ulcers are multiple, superficial erosions which occur mainly in the fundus and body of the stomach. They develop after shock, sepsis, and trauma and are often found in patients with peritonitis and other

chronic medical illness. Stress ulcers should be differentiated from reactivation of chronic duodenal or gastric ulcers, Cushing's ulcer following head injury, or drug-induced gastritis. Digestive symptoms are usually absent, hemorrhage is the most common manifestation, and perforation and obstruction are rare. The presence of luminal acid and ischemia are necessary for the production of stress ulcer, while disruption of the gastric mucosal barrier by refluxed duodenal content may contribute to the pathogenesis. Endoscopy is the mainstay of the diagnostic procedure, and angiography should be used if endoscopy fails to identify the bleeding lesions. Medical management should include volume replacement, nasogastric aspiration, and the use of antacid. Selective intraarterial infusion of pitressin has shown encouraging preliminary results. Surgical treatment is reserved only for those patients who continue to bleed despite all medical management. The operation of choice is open to question. We prefer vagotomy, pyloroplasty, and oversewing the ulcers as an initial operation. Since the result of all forms of therapy has been poor, it seems reasonable to try to prevent ulcer development. The use of vitamin A, hyperalimentation, and growth hormones is still in an experimental stage. Large clinical studies with case control are necessary before recommendations can be made. The use of potent and frequent antacid to buffer the gastric content has shown promising results; however, these observations need to be confirmed in a properly controlled and randomized study.

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Newer Concepts in the Pathogenesis of Peptic Ulcer Disease

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The traditional views of the pathophysiology of peptic ulcer disease consider duodenal ulcer as a disease of excessive acid secretion and gastric ulcer as a defect in gastric mucosal resistance. Clinically these relationships seem well-founded. Gastric ulcer occurs in the setting of chronic gastritis; healing can be enhanced by bismuth and carbenoxolone, drugs which do not have anti-secretory properties; and gastric ulcer is treated by resecting the antrum, the site of ulceration. On the other hand, duodenal ulcer patients have higher than normal rates of acid secretion to all known stimuli and are treated surgically by reducing acid secretion without removing the site of ulceration.

In this review the experimental evidence cited will follow these traditional lines; however, areas presently not well understood such as duodenal mucosal resistance may provide future insights into the pathogenesis of peptic ulcer disease.

DUODENAL ULCER

Three factors may play a role in the pathophysiology of duodenal ulcer disease: increased capacity to secrete acid, increased responsiveness to stimuli of acid secretion, and defective inhibition of acid secretion.

Increased Capacity to Secrete Acid

A large number of studies have been done to determine whether ulcer patients secrete more acid than normal subjects and to correlate the rates of acid secretion with disease activity or severity. Duodenal

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Table 1. *Gastric Acid Secretion in Man**

	BASAL ACID OUTPUT (mEq PER HR)			PEAK 30 MIN OUTPUT (mEq)		
	N†	DU	GU	N	DU	GU
Lopes, 1959	2.0	5.3	1.3	6.0	10.0	7.0
Sircus, 1960	2.5	6.0	2.1	11.2	18.8	7.3
Baron, 1963	1.3	3.6	1.9	10.8	21.0	11.3
Marks, 1963	4.2	7.1	4.3	11.3	17.6	9.8
Wormsley, 1965	1.8	2.1	1.5	17.2	21.2	14.5

*Data taken from Wormsley, K., and Grossman, M.: Maximal histalog test in control subjects and patients with peptic ulcer. Gut, 6:427–435, 1965.

†N = normal, DU = duodenal ulcer, GU = gastric ulcer.

ulcer patients have a higher mean basal acid output (BAO) and maximal acid output (MAO) than normal controls. However, there is considerable overlap. In a series of men with acute or chronic duodenal ulcer, with or without complications, the mean BAO was 2.1 mEq per hr and mean MAO 39.3 mEq per hr.[75] Mean values in age and sex-matched controls were 1.8 and 30.9 respectively. Other series have reported greater differences between ulcer and nonulcer patients (Table 1). Acid output, both BAO and MAO, fluctuates in individual patients. In one study BAO decreased after gastrointestinal hemorrhage or following a severe and protracted exacerbation, but in most cases no specific factors have been identified which account for changing secretory rates.[39] The degree of acid secretion does not correlate with the length of history of ulcer disease, level of activity, or occurrence of ulcer complications.[75] Lam and Sircus found that duodenal ulcer patients with a history of perforation or bleeding were more likely to be normal secretors rather than hypersecretors.[34] Pepsin output may be a more accurate discriminant of ulcer activity than acid secretion. Several studies have shown higher rates of pepsin output in patients with active ulcer disease compared with those in remission.[17, 67]

The higher rate of acid secretion in duodenal ulcer is highly correlated with a large parietal cell mass. In an autopsy study Cox found that duodenal ulcer patients had large stomachs with increased numbers of parietal cells.[13] The number of parietal cells per surface area of mucosa obtained by biopsy increases as MAO increases.[59] Card and Marks reported a strong correlation between the MAO before and after gastric resection and the number of parietal cells resected.[8] Some authors have criticized this study because the patients also had antrectomy which alone reduces parietal cell responsiveness.[73] However, the effect of antrectomy is constant from patient to patient and would affect only the absolute and not the relative changes observed by Card and Marks.

Duodenal ulcer patients then have higher maximal rates of acid secretion because of their large parietal cell mass. This feature may be more important in those individuals with very high MAO, greater than 50 mEq per hr, as they have an increased frequency of peptic ulcer disease.[19] The average duodenal ulcer patient, however, secretes at max-

imal rate for only short periods after a meal; otherwise, secretion is clearly submaximal.

Increased Responsiveness to Stimuli of Acid Secretion

Duodenal ulcer patients secrete more acid in response to all known types of stimuli including intravenous calcium and steak meal.[22, 53] This is not merely a function of their greater maximal acid output, for the difference between duodenal ulcer and normal persists when acid output is expressed as a percent of MAO.[22] Isenberg et al. reported that the dose of pentagastrin which produced half maximal secretion (D50) was significantly lower in duodenal ulcer patients than in controls, indicating increased sensitivity.[29]

The mechanism of this increased responsiveness is unknown, but may be due to an increased vagal and/or hormonal drive to secretion. It has been suggested that duodenal ulcer patients have an increased vagal tone. This cannot be measured directly but enhanced tone would presumably affect basal secretion and the response to sham feeding. The BAO is higher in duodenal ulcer and as MAO increases, the BAO/MAO ratio increases, suggesting increased drive. However, the BAO/MAO ratio is not different in duodenal ulcer and normal.[75] Sham feeding presumably provides pure vagal stimulation, but conflicting results have been reported for sham feeding studies in duodenal ulcer patients.[35, 42] Although vagotomy alone reduces acid secretion and usually cures ulcer disease, this effect is nonspecific. Vagotomy reduces acid secretion to all types of stimuli and to the same degree in patients with duodenal or gastric ulcer.[19] In addition, pharmacologic vagotomy with hexamethonium and atropine inhibits basal and maximal acid secretion to the same degree in duodenal ulcer patients and normal controls.[60] Until vagal tone can be directly measured the role of the vagus in the pathogenesis of duodenal ulcer disease cannot be determined.

The hormone gastrin may be responsible for the increased acid secretion in duodenal ulcer. Although basal serum gastrin concentrations are normal in duodenal ulcer, the meal-induced gastrin outputs are significantly greater than normal.[43] This is not due to an increased gastrin cell mass as the antral gastrin content is similar in duodenal ulcer and normal.[41] The enhanced meal response is probably due to defective regulation of gastrin release. Gastric acid inhibits gastrin release either directly on the antral G-cell or indirectly by stimulating gastrin-inhibitors from the intestine such as secretin.[68] It was shown that the inhibitory effect of acidification was defective in duodenal ulcer. An amino acid meal at pH 2.5 produced greater inhibition of acid secretion and gastrin release in normal than in duodenal ulcer.[68]

Multiple molecular forms of gastrin are present in circulation and differences in composition may exist between duodenal ulcer and normal. It was recently reported that duodenal ulcer patients have a greater proportion of G-17, the most potent component of gastrin, in the fasting and fed state as compared to normal.[62]

The relationship of basal acid secretion and basal gastrin concentration has interested many investigators. As duodenal ulcer patients have higher BAO and lower antral pH than normal, one would expect the

basal gastrin to be lower in duodenal ulcer than normal. This is not the case, though, and supports the theory of impaired inhibition. Petersen et al. have found that duodenal ulcer patients have a positive correlation between basal serum gastrin concentration and the D50 to pentagastrin.[51] The duodenal ulcer patients with a low D50, indicating increased sensitivity to pentagastrin, had low basal serum gastrin. Further studies are required to compare gastrin outputs following a meal with D50 to pentagastrin. It may be that duodenal ulcer patients are heterogenous; some exhibit increased sensitivity, perhaps due to increased vagal tone, while others have increased basal and stimulated gastrin concentrations.

Defective Acid Inhibition

Intestinal mechanisms have been shown to inhibit acid secretion. Acid, fat, and hypertonic solutions when instilled into the duodenum decrease pentagastrin-stimulated acid secretion.[1, 4, 32, 70, 72] Acid secretion was inhibited by instillation of 40 to 60 mEq per hr of 0.1N HCl into the duodenum but not by instillation of the subject's own gastric juice.[1] However, there is no evidence that this mechanism is defective in duodenal ulcer; acid, fat, and hypertonic glucose and saline inhibited acid secretion to a similar degree in duodenal ulcer and normal.[4, 32, 70, 72]

Pancreatic secretion of bicarbonate efficiently neutralizes HCl so that the pH distal to the pancreatic duct is around 6. A defect in bicarbonate secretion in duodenal ulcer would expose the duodenal mucosa to a more acidic milieu. Duodenal ulcer patients, however, do not have pancreatic insufficiency—the bicarbonate output in response to exogenous secretin is normal or increased. Petersen found that duodenal ulcer patients with a higher mean acid output also had higher mean bicarbonate output than control.[52] There is dispute regarding bicarbonate secretion following duodenal acidification in duodenal ulcer. Wormsley reported that duodenal ulcer patients secreted less HCO_3 than normal and Bloom and Ward found that the serum secretin concentration after acidification was lower in duodenal ulcer than normal.[3, 74] However Cano et al. observed a similar bicarbonate output and secretin release in duodenal ulcer and normal following duodenal instillation of graded amounts of acid.[7]

Similarly conflicting results are reported for measurement of duodenal pH. Archanbault found lower fasting duodenal bulb pH in duodenal ulcer than normal, while Rhodes noted similar postprandial pH in both groups.[54, 55] Rune reported a lower bulb pH in duodenal ulcer but similar postbulbar pH in duodenal ulcer and normal.[57]

There is no convincing evidence that defective inhibition of acid secretion is an important factor in the development of duodenal ulcer.

Gastric Emptying

The results of gastric emptying studies in duodenal ulcer disease are variable due to the nature of the test meal, liquid or solid, calorie or noncalorie containing. Griffith et al. measured gastric emptying of a meal of milk, porridge, egg, and bread labeled with ^{51}Cr and found that duodenal ulcer patients empty faster than normal, $T_{1/2}$ of 55 vs. 65

minutes.[28] The result of rapid emptying of a meal is to decrease its buffering ability. Fordtran and Walsh noted that the amount of meal buffer present in the stomach 2 hours after ingestion in duodenal ulcer was less than half that of normal.[22] Cano and Isenberg measured acid secretion and gastric emptying of a protein meal in duodenal ulcer and normal subjects.[6] The duodenal ulcer patients had significantly greater acid output than normal and emptied gastric contents more rapidly. This resulted in a greater acid load to the duodenum in duodenal ulcer patients.

In summary, duodenal ulcer patients not only have a greater than normal maximal secretory capacity, but more importantly, they secrete at higher than normal rates with submaximal stimuli. A dual defect is present during meal-stimulated secretion. Impaired antral inhibition of gastrin release contributes to excessive acid secretion and rapid gastric emptying reduces the buffering effect of the meal itself. The result is a large acid load to the duodenum where inhibitory mechanisms and pancreatic secretion are not sufficient to control the acid secretion.

GASTRIC ULCER

Three types of gastric ulcer have been described by Johnson: type I, single ulcers on the lesser curve; type II, gastric ulcers associated with duodenal ulcers; and type III, prepyloric ulcers.[31] Type I represented 57 per cent of his series of 5000 cases and was associated with hyposecretion of acid; types II and III were equally divided and were associated with hypersecretion. The pathophysiologic features of gastric ulcer may not apply equally to all three types.

Ulcer Location

Oi et al. in 1969 proposed a "dual control mechanism" for the etiology of gastric ulcers based on observations of the surrounding mucosa and underlying musculature in a series of 366 gastric ulcer specimens obtained surgically.[47] They reported that gastric ulcers occur in antral mucosa adjacent to acid-secreting fundic mucosa. This was true in 96 per cent of type I and 82 per cent of type II ulcers. Further, 97 per cent of gastric ulcers were located in an area which was crossed by a broad circular muscle, an area representing only 11 per cent of the entire stomach. In fact, all but one type I gastric ulcer were found at a fundoantral border crossed by this circular muscle band. The sole exception was an ulcer occurring in ectopic antral mucosa. They postulated that this area was one of severe kinetic strain due to gastric contractions.

Gastritis occurs in most patients with gastric ulcer. It invariably affects the antrum but also may extend into the body of the stomach.[54] McDonald observed that of 51 patients with gastric ulcer, 44 had abnormal antral mucosa characterized by cellular infiltration of the lamina propria, loss of epithelial mucus, atrophy of pyloric glands, and intestinal metaplasia.[40] The seven patients with normal antral mucosa were all habitual aspirin users.

There is some debate as to whether the gastritis produces or is due

to the gastric ulcer. Experimentally, mucosa affected by gastritis is more susceptible to ulceration from peptic digestion.[54] In an endoscopic study of gastric ulcer before and after healing, it was noted that gastritis persisted in the majority of patients despite healing of the ulcer.[26]

Gastric Mucosal Barrier

Gastric mucosa has the unique capacity to maintain an enormous concentration gradient between lumen and plasma hydrogen ion concentration, over one million to one. This has been called the mucosal barrier to back diffusion of hydrogen. Agents such as aspirin, bile salts, ethanol, and lysolecithin are barrier breakers.[30] When instilled into the stomach in an acidic solution, they produce back diffusion of hydrogen into the mucosa and this leads to edema, hemorrhage, and erosions. However, acute gastric erosions may occur in the absence of measurable back diffusion during hemorrhagic shock in dogs and restraint stress in rats.[27, 46]

In man, Overholt and Pollard found that instillation of acid into the stomach produced significantly more back diffusion in patients with gastric ulcer than in controls or duodenal ulcer patients.[48] This was confirmed by Chapman et al. and in two cases back diffusion persisted despite healing of the gastric ulcer.[9]

Bile Reflux

An attractive hypothesis for the pathogenesis of gastric ulcer is that reflux of bile acid, and possibly lysolecithin, into the stomach breaks the mucosal barrier and produces increased hydrogen back diffusion leading to mucosal inflammation and possibly to chronic gastritis. Du Plessis was the first to confirm that fasting gastric ulcer patients have greater than normal concentration of bile acids in the stomach.[16] In another study radiolabeled bile acids were measured in gastric contents in the fasting and fed state.[55] Gastric ulcer and normal subjects had similar fasting concentrations, but, following a liquid meal, a greater than tenfold difference existed between gastric ulcer and normal. However, bile acid reflux is not seen in all patients with gastric ulcer. Black and his associates found that up to 50 per cent of gastric ulcer patients have fasting and postprandial bile acid concentrations which overlap with nonulcer subjects.[2] In addition, increased bile reflux is reported in conditions without gastric ulcer, such as gastroesophageal reflux and following pyloroplasty.[54]

It has been suggested that pyloric sphincter incompetence is present in gastric ulcer and this promotes bile reflux. Valenzuela et al. reported that gastric ulcer patients have a lower basal sphincter pressure than control and duodenal ulcer subjects,[66] and Fisher and Cohen noted that pyloric sphincter pressure in gastric ulcer patients did not increase in response to secretin, cholecystokinin, intraduodenal amino acids, or fat.[18] Cigarette smoking, which has been shown to increase bile reflux, decreases resting sphincter pressure.[54, 66] However, some investigators have been unable to confirm the existence of a pyloric high pressure zone, and more studies are required to determine the place of pyloric sphincter incompetence in gastric ulcer.[33]

Acid and Emptying

Dragstedt and Woodward theorized that gastric ulcer was caused by antral stasis due to impaired gastric emptying leading to distention of the antrum, gastrin release, and hyperacidity.[15] Indeed, in animals creation of pyloric stenosis or obstruction produces increased acid secretion and gastric ulceration.[54] In man, vagotomy without adequate drainage caused gastric stasis and ulceration.

However, most patients with gastric ulcer do not conform to this hypothesis. In Griffith's study of gastric emptying, patients with type I gastric ulcer had normal gastric emptying rate and type II patients tended to have slower emptying times but overlapped with normal controls.[28]

Both basal and maximal acid secretion is lower than normal in type I gastric ulcer, whereas types II and III are similar to normal.[75] The tendency for low rates of acid secretion are most likely a consequence of gastritis and back diffusion. Fasting serum gastrin concentrations are higher in gastric ulcer than in normal and duodenal ulcer, but this appears to be due to the higher antral pH in gastric ulcer.[65] Thus, most gastric ulcer patients do not have evidence of impaired gastric emptying or acid hypersecretion.

Local Factors

Bile reflux could account for the gastritis which accompanies gastric ulcer, but the specific site of ulceration may be determined by local factors such as blood flow, cell turnover, and mucus. The characteristic location of gastric ulcer on the lesser curvature of the stomach may reflect Oi's hypothesis, but also the blood supply to the lesser curve differs from the main stomach. The mucosal arteries to the anterior and posterior walls derive from a plexus of vessels beneath the muscularis mucosae; the lesser curve is supplied by arteries arising from the left gastric artery outside the stomach wall.[20]

Gastric epithelial cells may be important defensive factors in gastric ulcer disease. They have a short life span, averaging 4 days, and are continually undergoing replication, shedding and renewal.[69] During restraint stress in rat cell replication is decreased and as epithelial cells are extruded into the lumen without replacement erosions occur.[38]

The epithelial cells contain mucus, a highly viscous solution with a limited capacity to neutralize acid. The deep mucus cells in the neck of gastric glands secrete sulphated glycoproteins which form a complex with cellular protein that is resistant to peptic digestion.[5] This complex may act as an inhibitor to pepsin, and in fact, after histamine stimulation mucosal cells have an increased content of this complex.[5] However, in man, sulphated glycoproteins are found in salivary and esophageal but not gastric secretions. Anti-inflammatory drugs such as cortisone, aspirin, and indomethacin decrease mucus secretion, whereas carbenoxolone, a drug which increases gastric ulcer healing rate, promotes mucous secretion and prolongs epithelial cell life span.[38] Mucus may have a limited role as an antipeptic substance. However, patients with peptic ulcer do not have a deficiency in gastric mucous secretion or an abnormality in the concentration of any of the constituents of mucus.[20]

In summary, gastric ulceration may result when local defense mechanisms such as mucous secretion, cell renewal, or blood supply are defective. Bile reflux and back diffusion of hydrogen may be necessary preconditions to initiate gastritis and predispose the mucosa to ulceration.

DRUGS ASSOCIATED WITH PEPTIC ULCER DISEASE

Peptic ulcer disease has been associated with a variety of drugs, particularly anti-inflammatory agents, but to determine whether a true association exists it is necessary to know the frequency of peptic ulcer diseases in the general population.

In an autopsy study conducted at Leeds in England the frequency of peptic ulcer was 14.2 per cent for men and 7.7 per cent for women.[71] Doll et al., from a field survey, reported lower frequencies of 5.8 per cent for men and 1.9 per cent for women.[14] The true frequencies should lie between those from the accurate but selective autopsy study and the less accurate but more representative field survey.

Salicylates

The difficulties of showing an association between peptic ulcer disease and drug ingestion are compounded when studying aspirin. Subjects often fail to remember casual aspirin ingestion or may not realize that a particular compound contains aspirin. This accounts for the wide variation seen in reported frequencies of aspirin use in control populations, 4 to 44 per cent.[36] Ulcer patients, however, are more aware of aspirin ingestion, and there is less variation in their reported frequencies of aspirin use. It is difficult to avoid this bias in studies which compare aspirin use in patients with ulcer disease to control populations.

Unbuffered aspirin causes an increased occult blood loss in most individuals, 4 ml a day vs 1.5 in controls.[11] However, aspirin provokes no greater blood loss in ulcer patients than in controls.[50]

Aspirin has been associated with major gastrointestinal hemorrhage. Langman reviewed eight series in which aspirin ingestion was always more frequent in patients with hemorrhage than in controls.[36] However, it was not possible to determine whether aspirin use preceded the onset of bleeding. In a recent study Levy has attempted to answer this question. He compared the frequency of heavy (4 or more days a week), regular (for 3 months previous) aspirin ingestion in patients with newly diagnosed major gastrointestinal bleeding without an antecedent predisposing cause to a control population. He found that 16 per cent of bleeding patients had heavy aspirin use as compared to 7 per cent of controls, a significant difference.[37] He concluded that heavy aspirin use was associated with hemorrhage, but the incidence of hospital admissions for bleeding in heavy aspirin users is low, 15 per 100,000 per year.

The association of aspirin use with gastric ulcerations has been documented by several studies.[25, 37] Aspirin produces increased hydrogen back diffusion in animals and man, a factor which may be of im-

portance in the development of gastric lesions.[30] More specifically, aspirin use has been associated with the development of a particular type of gastric ulcer. McDonald reported that gastric ulcer without attendant antral gastritis was found only in aspirin users.[40]

There is no evidence of an association of aspirin use with duodenal ulcer.[11, 37]

Corticosteroids

Some investigators have felt that patients on steroid therapy may develop an antral ulcer which is frequently asymptomatic and often perforates.[61] It was thought to have distinct histologic and radiologic features, but a careful controlled study of steroid ulcers failed to discover any typical features as compared to nonsteroid ulcers.[24]

The literature was surveyed in 1954 by Sandweiss,[58] in 1967 by Cooke,[12] and in 1975 by Conn and Blitzer[10] with the same result; corticosteroid therapy did not increase the incidence of peptic ulcer disease. Conn and Blitzer did note that an association might depend on dose; patients receiving a total dose of greater than 1000 mg prednisone developed peptic ulcer more frequently than those receiving less.

Corticosteroids may delay healing rate but this has not been studied in man. Steroids do not increase fecal blood loss and do not increase hydrogen back diffusion in animals.[11]

Other Agents

Indomethacin increases hydrogen back diffusion and fecal blood loss.[11] In the only prospective study of chronic indomethacin therapy, the incidence of peptic ulcer disease was less than 3 per cent.[56]

Phenylbutazone does not break the barrier and it does not increase occult blood loss. Several retrospective studies have failed to detect an association of phenylbutazone treatment with ulcer disease.[11]

Although ethanol breaks the barrier to back diffusion, a recent study by Friedman et al. found that alcohol consumption was not related to a history of peptic ulcer.[23] In the the same study coffee drinking was not associated with peptic ulcer; however, one study showed that college students who were heavy coffee drinkers were more likely to develop ulcer than nondrinkers.[49]

There is no convincing evidence that reserpine is ulcerogenic.[11]

Conclusion

In conclusion, only aspirin of the anti-inflammatory agents is associated with gastrointestinal pathology, namely gastric ulcer and upper gastrointestinal bleeding. However, there is no information available on the effect of these drugs on the course of ulcer disease, and cautious use of these agents in patients with known peptic ulcer disease is still warranted.

SUMMARY

This review has dealt mainly with the physiologic features of peptic ulcer disease. Space does not permit an adequate analysis of the epide-

miologic and psychosomatic aspects of peptic ulcer. The reader is referred to several excellent articles on these topics.[21, 44, 45, 63, 64]

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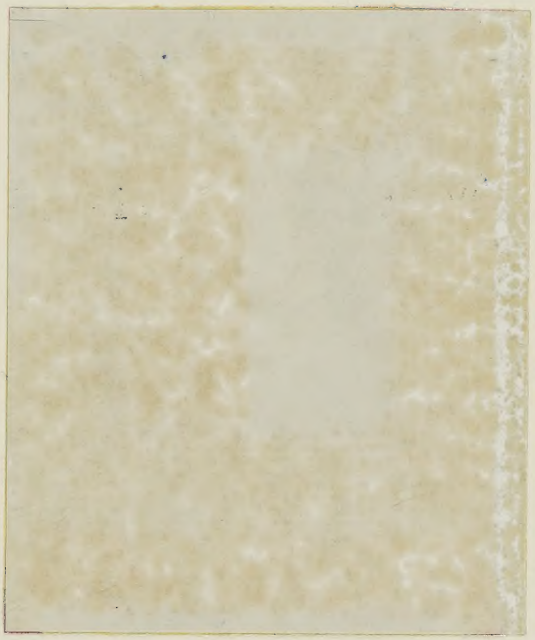

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